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(54) Title: 5-CYCLOALKENYL 5*H*-CHROMENO[3,4-F]QUINOLINE DERIVATIVES AS SELECTIVE PROGESTERONE RECEPTOR MODULATOR COMPOUNDS

(57) Abstract: The present invention is directed to compounds, pharmaceutical compositions, and methods for modulating processes mediated by Progesterone Receptor. Also provided are methods of making such compounds and pharmaceutical compositions.

5-CYCLOALKENYL *5H*-CHROMENO[3,4-*f*]QUINOLINE DERIVATIVES AS SELECTIVE PROGESTERONE RECEPTOR MODULATOR COMPOUNDS

Field of the Invention

This invention relates to nonsteroidal 5-cycloalkenyl 5H-chromeno[3,4-f]quinoline derivatives that may be modulators (*i.e.*, agonists, partial agonists and antagonists) of progesterone receptors and to methods for the making and use of such compounds.

Background of the Invention

Progesterone receptor (PR) modulators have been widely used in regulation of female reproduction systems and in treatment of female hormone dependent diseases. The effectiveness of known steroidal PR modulators is often tempered by their undesired side-effect profile, particularly during long-term administration. For example, the effectiveness of synthetic progestins, such as norgestrel, as female birth control agents must be weighed against the increased risk of breast cancer and heart disease. Similarly, the progesterone antagonist, mifepristone (RU486), if administered for chronic indications, such as uterine fibroids, endometriosis and certain hormone-dependent cancers, could lead to homeostatic imbalances in a patient due to its inherent cross-reactivity as a glucocorticoid receptor (GR) antagonist. Accordingly, identification of compounds that have good receptor-selectivity for PR over other steroid hormone receptors as well as good tissue-selectivity (e.g., selectivity for uterine tissue over breast tissue) would be of significant value in the improvement of women's health.

A group of nonsteroidal molecules, which contain a di- or tetra-hydroquinoline ring as core pharmacophore (Todd, Jones; *et al.* US Patent Nos. 5,693,646; 5,693,647

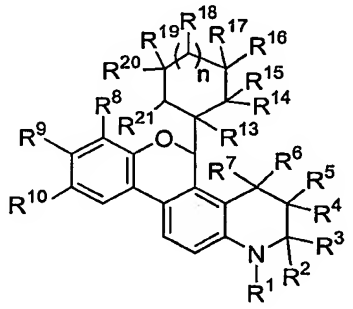
and 5,696,127) (M.J. Coghlan *et al.*, PCT Publication Nos. WO 99/41256 A1 and WO 99/41257 A1) have been described as steroid receptor modulator compounds.

The entire disclosures of the publications and references referred to herein are incorporated by reference herein and are not admitted to be prior art.

Summary of the Invention

The present invention is directed to compounds, pharmaceutical compositions, and methods for modulating processes mediated by Progesterone Receptor. More particularly, the invention relates to nonsteroidal compounds and compositions which may be high affinity, high specificity agonists, partial agonists (*i.e.*, partial activators and/or tissue-specific activators) and/or antagonists for progesterone receptors. Also provided are methods of making such compounds and pharmaceutical compositions.

Compounds of the present invention may be represented by the formulae:



(I)

wherein:

R^1 is selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 haloalkyl, C_1–C_4 heteroalkyl, COR^{11}, CO_2R^{11}, SO_2R^{11}, and $CONR^{11}R^{12}$;

R^2 and R^3 each independently is selected from the group of hydrogen, C_1–C_6 alkyl, and C_1–C_6 haloalkyl; or

R^2 and R^3 taken together form a cycloalkyl ring of from three to twelve carbons;

R^4 through R^7 each independently is selected from the group of hydrogen, F, Cl, Br, CN, OR^{11}, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl; or

R^5 and R^7 taken together form a bond; or

R^6 and R^7 taken together are selected from the group of methylidene, mono-substituted methylidene, di-substituted methylidene and carbonyl;

R^8 through R^{10} each independently is selected from the group of hydrogen, F, Cl, Br, I, NO_2, CN, OR^{11}, $NR^{11}R^{12}$, SR^{11}, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, C_1–C_8 alkyl, C_1–C_8 heteroalkyl, C_1–C_8 haloalkyl, allyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl;

R^{11} and R^{12} each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^{13} is hydrogen; or

R^{13} and R^{14} taken together form a bond;

R^{14} through R^{20} each independently is selected from the group of hydrogen, F, Cl, Br, OR^{11}, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl; or

R^{14} and R^{15} taken together are selected from the group of methylidene, carbonyl and thiocarbonyl; or

R^{16} and R^{17} taken together are selected from the group of methylidene, mono-substituted methylidene, di-substituted methylidene, carbonyl and thiocarbonyl; or

R^{14} and R^{16} taken together form a bond or "–O–" bridge; or

R^{16} and R^{18} taken together form a bond when n is 1; or

R^{16} and R^{19} taken together form a bond when n is 0;

R^{21} is hydrogen; or

R^{21} and R^{20} taken together form a bond;

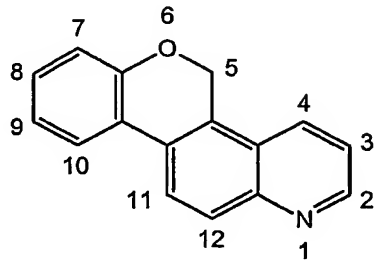
n is 0, 1, 2, or 3;

and pharmaceutically acceptable salts and prodrugs thereof.

Definitions and Nomenclature

As used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise. Furthermore, in an effort to maintain consistency in the naming of compounds of similar structure but differing substituents, the compounds described herein are named according to the following general guidelines. The numbering system for the location of substituents on such compounds is also provided.

A 5*H*-chromeno[3,4-*f*]quinoline is defined by the following structure:



The term "alkyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain or cyclic-chain alkyl radical having from 1 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having from 1 to about 6 carbon atoms as well as those having from 1 to about 4 carbon atoms. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-amyl, pentyl, hexyl, heptyl, octyl and the like.

The term "alkenyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon double-bonds and having from 2 to about 18 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon double bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, 1,3-butadienyl and the like.

Methylidene, alone or in combination, refers to $=CH_2$ and may be optionally substituted.

Allyl, alone or in combination, refers to $-CH_2-CH=CH_2$ and may be optionally substituted.

The term "alkynyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon triple-bonds and having from 2 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon triple bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, butynyl and the like.

The term "heteroalkyl" refers to alkyl groups, as described above, in which one or more skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof. The term heteroalkyl also includes alkyl groups in which one 1 to about 6 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof, as well as those in which 1 to 4 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof and those in which 1 to 2 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof.

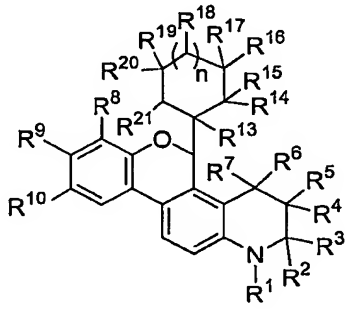
The term "halogen" includes F, Cl, Br and I.

The term "mediate" means affect or influence. Thus, for example, conditions mediated by a progesterone receptor are those in which a progesterone receptor plays a role. Progesterone receptors are known to play a role in conditions including, for example, infertility, contraception, pregnancy maintenance and termination, female hormone deficiency, female sexual dysfunction, dysfunctional uterine bleeding, endometriosis, mood disorder, osteoporosis, and hormone-dependent cancers.

The term "selective" refers to compounds that display reactivity towards a particular receptor *(e.g.*, a progesterone receptor) without displaying substantial cross-reactivity towards another receptor (*e.g.*, glucocorticoid receptor). Thus, for example, selective compounds of the present invention may display reactivity towards progesterone receptors without displaying substantial cross-reactivity towards other steroid hormone receptors.

Detailed Description of the Invention

Compounds of the present invention may be represented by the formulae:



(I)

wherein:

R^1 is selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 haloalkyl, C_1–C_4 heteroalkyl, COR^{11}, CO_2R^{11}, SO_2R^{11}, and $CONR^{11}R^{12}$;

R^2 and R^3 each independently is selected from the group of hydrogen, C_1–C_6 alkyl, and C_1–C_6 haloalkyl; or

R^2 and R^3 taken together form a cycloalkyl ring of from three to twelve carbons;

R^4 through R^7 each independently is selected from the group of hydrogen, F, Cl, Br, CN, OR^{11}, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl; or

R^5 and R^7 taken together form a bond; or

R^6 and R^7 taken together are selected from the group of methylidene, mono-substituted methylidene, di-substituted methylidene and carbonyl;

R^8 through R^{10} each independently is selected from the group of hydrogen, F, Cl, Br, I, NO_2, CN, OR^{11}, $NR^{11}R^{12}$, SR^{11}, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, C_1–C_8 alkyl, C_1–C_8 heteroalkyl, C_1–C_8 haloalkyl, allyl, C_2–C_8 alkenyl and C_2–C_8 alkynyl;

R^{11} and R^{12} each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^{13} is hydrogen; or

R^{13} and R^{14} taken together form a bond;

R^{14} through R^{20} each independently is selected from the group of hydrogen, F, Cl, Br, OR^{11}, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl; or

R^{14} and R^{15} taken together are selected from the group of methylidene, carbonyl and thiocarbonyl; or

R^{16} and R^{17} taken together are selected from the group of methylidene, mono-substituted methylidene, di-substituted methylidene, carbonyl and thiocarbonyl; or

R^{14} and R^{16} taken together form a bond or "–O–" bridge; or

R^{16} and R^{18} taken together form a bond when n is 1; or

R^{16} and R^{19} taken together form a bond when n is 0;

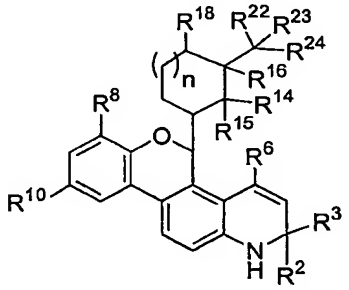
R^{21} is hydrogen; or

R^{21} and R^{20} taken together form a bond;

n is 0, 1, 2, or 3;

and pharmaceutically acceptable salts and prodrugs thereof.

Compounds of the invention include those represented by the formulae:



(II)

wherein:

R^2 and R^3 each independently is selected from the group of hydrogen, C_1–C_4 alkyl, and C_1–C_4 haloalkyl;

R^6 is selected from the group of hydrogen, F, Cl, Br, CN, OR^{11}, C_1–C_4 alkyl, and C_1–C_4 haloalkyl;

R^8 and R^{10} each independently is selected from the group of hydrogen, F, Cl, Br, CN, OR^{11}, $NR^{11}R^{12}$, SR^{11}, COR^{11}, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, C_1–C_4 haloalkyl, allyl, and C_2–C_4 alkenyl;

R^{11} and R^{12} each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^{14}, R^{15}, R^{18}, R^{22}, R^{23}, R^{24} each independently is selected from the group of hydrogen, F, Cl, OR^{11}, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl;

R^{22}, R^{23}, R^{24} together consists of not more than 3 carbon atoms;

R^{16} taken together with one of R^{14}, R^{18}, and R^{22} form a bond or "–O–" bridge;

n is 0, 1, 2, or 3;

and pharmaceutically acceptable salts and prodrugs thereof.

In one aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a progesterone receptor modulator compound according to any one of formulae I through II shown above wherein R^1 through R^{24}, and n all have the same definitions as given above.

In another aspect, the present invention comprises a method of modulating processes mediated by progesterone receptors comprising administering to a patient an effective amount of a compound according to any one of the formulae I through II shown above, wherein R^1 through R^{24}, and n all have the same definitions as those given above.

Any of the compounds of the present invention can be synthesized as pharmaceutically acceptable salts for incorporation into various pharmaceutical compositions. As used herein, pharmaceutically acceptable salts include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, hydrofluoric, sulfuric, citric, maleic, acetic, lactic, nicotinic, succinic, oxalic, phosphoric, malonic, salicylic, phenylacetic, stearic, pyridine, ammonium, piperazine, diethylamine, nicotinamide, formic, urea, sodium, potassium, calcium, magnesium, zinc, lithium, cinnamic, methylamino, methanesulfonic, picric, tartaric, triethylamino, dimethylamino, and tris(hydroxymethyl)aminomethane. Additional pharmaceutically acceptable salts are known to those skilled in the art.

The PR agonist, partial agonist and antagonist compounds of the present invention may be particularly useful for female hormone replacement therapy and as modulators of fertility (*e.g.*, as contraceptives, contragestational agents or abortifacients, *in vitro* fertilization, pregnancy maintenance), either alone or in conjunction with one or more estrogen receptor modulators. The PR modulator compounds of this invention may be also used in the treatment of dysfunctional uterine bleeding, dysmenorrhea, endometriosis, leiomyomas (uterine fibroids), hot flushes, mood disorders, and meningiomas. The PR modulator compounds of this invention also may be used in the treatment of various hormone-dependent cancers, including, without limitation, cancers of ovaries, breast, endometrium and prostate. The PR modulator compounds of this invention can also be used in treatment of female osteoporosis, either alone or in combination with one or more estrogen receptor modulators.

It will be understood by those skilled in the art that while the compounds of the present invention will typically be employed as a selective agonists, partial agonists or antagonists, that there may be instances where a compound with a mixed steroid receptor profile is preferred. For example, use of a PR agonist (*i.e.*, progestin) in female contraception often leads to the undesired effects of increased water retention and acne flare ups. In this instance, a compound that is primarily a PR agonist, but also displays some AR and MR modulating activity, may prove useful. Specifically, the mixed MR effects would be useful to control water balance in the body, while the AR effects would help to control any acne flare ups that occur.

Furthermore, it will be understood by those skilled in the art that the compounds of the present invention, including pharmaceutical compositions and formulations containing these compounds, can be used in a wide variety of combination therapies to treat the conditions and diseases described above. Thus, the compounds of the present invention can be used in combination with other hormones and other therapies, including, without limitation, chemotherapeutic agents such as cytostatic and cytotoxic agents, immunological modifiers such as interferons, interleukins, growth hormones and other cytokines, hormone therapies, surgery and radiation therapy.

Representative PR modulator compounds (*i.e.*, agonists, partial agonists and antagonists) according to the present invention include:

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **24**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **25**);

(+)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **27**);

(-)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **28**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **29**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **30**);

(+)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **32**);

(-)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **33**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **34**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **35**);

(+)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **37**);

(-)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **38**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-methoxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **39**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **41**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **42**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclopentenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **44**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclopentenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **45**);

(±)-(*5l,1'l*)-5-(3,5,5-trimethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **47**);

(±)-(*5l,1'u*)-5-(3,5,5-trimethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **48**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **50**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **51**);

(±)-5-(3-methyl-3-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **52**);

(±)-5-(2-cyclopenta-1,3-dienyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **53**);

(±)-(*5l,1'l*)-5-(3-ethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **55**);

(±)-(*5l,1'u*)-5-(3-ethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **56**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-7-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **58**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclohexenyl)-7-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **59**);

(±)-(*5l,1'l*)-5-(3-ethyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **61**);

(±)-(*5l,1'l*)-5-(3-ethylidenecyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **62**);

(±)-(*5l,1'l*)-5-(3-methyl-3-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **63**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-8-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **64**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-8-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **65**);

(±)-(*5l,1'l*)-5-(2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **67**);

(±)-(*5l,1'u*)-5-(2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **68**);

(±)-5-(1-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **69**);

(±)-(*5l,1'l*)-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **71**);

(+)-(*5l,1'l*)-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **73**);

(-)-(*5l,1'l*)-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **74**);

(±)-(*5l,1'l*)-5-(2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **75**);

(±)-(*5l,1'u*)-5-(2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **76**);

(±)-(*5l,1'l*)-5-(2-cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-5*H*-chromeno[3,4-*f*]quinoline (compound **77**);

(±)-(*5l,1'l*)-5-(2-methylidenecyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **79**);

(±)-(*5l,1'u*)-5-(2-methylidenecyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **80**);

(±)-(*5l,1'l*)-5-(2-oxocyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **81**);

(±)-(*5l,1'u*)-5-(2-oxocyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **82**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-methoxy-1,2-dihydro-1,2,2,4-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **83**);

(±)-5-(2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **84**);

(±)-(*5l,1'l*)-5-(2,3-dimethyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **85**);

(±)-5-(3-methylidene-cyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **87**);

(±)-(*5l,1'u*)-5-(3-ethylidenecyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **88**);

(±)-(*5l,1'l*)- 5-(2-cycloheptenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound **89**);

(±)-*(5l,1'l)*- 5-(2-cyclooctenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound **91**);

(±)-*(5l,1'u)*- 5-(2-cyclooctenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound **92**);

(±)-*(5l,1'l)*- 5-(2,3-epoxy-3-methylcyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound **94**);

(±)-*(5l,1'l)*- 5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylene-5*H*-chromeno[3,4-f]quinolin-3-ol (Compound **95**);

(±)-*(5l,1'l)*- 5-(2,3-epoxy-2,3-dimethylcyclopentyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound **96**);

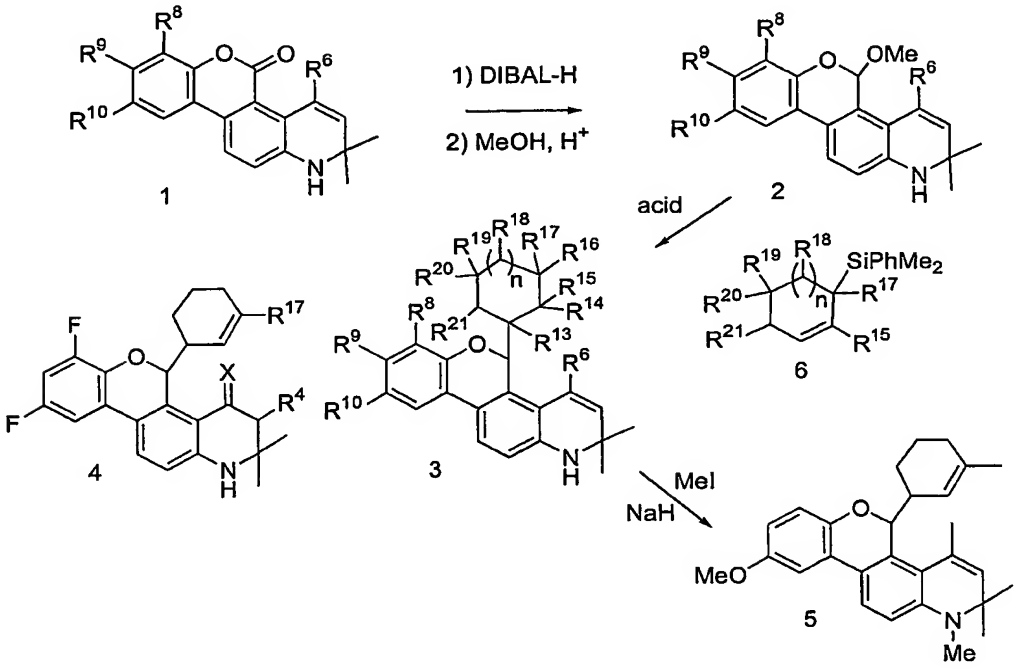
(±)-*(5l,1'u)*- 5-(2,3-epoxy-3-methylcyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound **97**); and

(±)-*(5l,1'l)*- 5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro-2,2-dimethyl-5*H*-chromeno[3,4-f]quinolin-4-one (Compound **98**).

The sequence of steps for the general schemes to synthesize the compounds of the present invention is shown below. In each of the Schemes the R groups (*e.g.*, R^1, R^2, *etc.*) correspond to the specific substitution patterns noted in the Examples. However, it will be understood by those skilled in the art that other functionalities disclosed herein at the indicated positions of compounds of formulae I and II also comprise potential substituents for the analogous positions on the structures within the Schemes. In a

further aspect, the present invention contains a novel process for the preparation of the compounds of the present invention.

Scheme I



Scheme I describes the synthesis of the 5-cycloalkenyl analogues **3**, **4** and **5**. Reduction of lactones **1**, which were prepared by the previously disclosed methods (Todd, Jones; *et al.* US Patent Nos. 5,693,646; 5,693,647 and 5,696,127), with DIBAL-H followed by acid catalyzed methylation provides lactal intermediates **2**. Treatment of the lactal **2** with a nucleophile, such as a cyclic allylsilane **6**, in the presence of a Lewis acid, such as BF_3-OEt_2, affords the final product **3**. Compound of structure **4** may also isolated as a minor product. Methylation of compound **3** with iodomethane in the presence of a base, such as sodium hydride, provides N-methylated product of structure **5**.

The compounds of the present invention also include racemates, stereoisomers and mixtures of said compounds, including isotopically-labeled and radio-labeled compounds. Such isomers can be isolated by standard resolution techniques, including fractional crystallization and chiral column chromatography.

As noted above, any of the PR modulator compounds of the present invention can be combined in a mixture with a pharmaceutically acceptable carrier to provide pharmaceutical compositions useful for treating the biological conditions or disorders noted herein in mammalian, and particularly in human patients. The particular carrier employed in these pharmaceutical compositions may take a wide variety of forms depending upon the type of administration desired. Suitable administration routes include enteral (*e.g.*, oral), topical, suppository, inhalable and parenteral (*e.g.*, intravenous, intramuscular and subcutaneous).

In preparing the compositions in oral liquid dosage forms (*e.g.*, suspensions, elixirs and solutions), typical pharmaceutical media, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be employed. Similarly, when preparing oral solid dosage forms (*e.g.*, powders, tablets and capsules), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like will be employed. Due to their ease of administration, tablets and capsules represent a desirable oral dosage form for the pharmaceutical compositions of the present invention.

For parenteral administration, the carrier will typically comprise sterile water, although other ingredients that aid in solubility or serve as preservatives may also be

included. Furthermore, injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like will be employed.

For topical administration, the compounds of the present invention may be formulated using bland, moisturizing bases, such as ointments or creams. Examples of suitable ointment bases are petrolatum, petrolatum plus volatile silicones, lanolin and water in oil emulsions such as Eucerin™, available from Beiersdorf (Cincinnati, Ohio). Examples of suitable cream bases are Nivea™ Cream, available from Beiersdorf (Cincinnati, Ohio), cold cream (USP), Purpose Cream™, available from Johnson & Johnson (New Brunswick, New Jersey), hydrophilic ointment (USP) and Lubriderm™, available from Warner-Lambert (Morris Plains, New Jersey).

The pharmaceutical compositions and compounds of the present invention will generally be administered in the form of a dosage unit (*e.g.*, tablet, capsule, etc.). The compounds of the present invention generally are administered in a daily dosage of from about 1 μg/kg of body weight to about 50 mg/kg of body weight. Typically, the compounds of the present invention are administered in a daily dosage of from about 2 μg/kg to about 25 mg/kg of body weight. Most often, the compounds of the present invention are administered in a daily dosage of from about 10 μg/kg to about 5 mg/kg body weight. As recognized by those skilled in the art, the particular quantity of pharmaceutical composition according to the present invention administered to a patient will depend upon a number of factors, including, without limitation, the biological activity desired, the condition of the patient, and tolerance for the drug.

The compounds of this invention also have utility when radio- or isotopically-labeled as ligands for use in assays to determine the presence of PR in a cell background or extract. They are particularly useful due to their ability to selectively activate progesterone receptors, and can therefore be used to determine the presence of such receptors in the presence of other steroid receptors or related intracellular receptors.

The compounds and pharmaceutical compositions of the present invention may be extremely potent activators of PR. For example, the compounds and compositions of the present invention may display 50% maximal activation of PR at a concentration of less than 50 nM. Some compounds and compositions of the present invention may display 50% maximal activation of PR at a concentration of less than 20 nM, and some may display such activity at a concentration of less than 10 nM.

The invention will be further illustrated by reference to the following non-limiting Examples.

EXAMPLE 1

Preparation of (±)-*(5l,1'l)*-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (±)-*(5l,1'u)*-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **24** and **25**, Structure **3** of Scheme I, where $R^8 = R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^{10} = F$, $R^6 = R^{17} =$ methyl, $R^{14}/R^{16} =$ a bond, n = 1)

These compounds were prepared according the following general procedure:

A mixture of a 5-methoxy-5*H*-chromeno[3,4-*f*]quinoline, such as 9-fluoro-2,2,4-trimethyl-5-methoxy-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinoline (compound **26**, Structure

2 of Scheme I, where $R^8 = R^9 = H$, $R^{10} = F$, R^6 = methyl), and a cyclic allylsilane derivative, such as 3-(dimethylphenylsilyl)-3-methyl-1-cyclohexene (Structure 6 of Scheme I, where R^{17} = methyl, $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, n = 1) (1.0-1.5 equiv.), in dry CH_2Cl_2 was cooled to –25°C, after which a Lewis acid such as $BF_3 \cdot Et_2O$ (excess) was added dropwise. The resulting mixture was stirred at –25°C for half an hour, then warmed up gradually to 0°C and quenched with slow addition of aqueous $NaHCO_3$ (concentrated). The reaction mixture was extracted with CH_2Cl_2 (3 x). The extracts were washed with brine, combined, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane:EtOAc, 9:1) afforded 40-90% of a diastereomeric mixture of the 5-alkenyl products, which then were separated by prep TLC or HPLC.

Compound **24** was isolated as the major isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.2, 1H), 7.29 (dt, J = 9.4, 3.1, 1H), 6.91 (dd, J = 8.6, 4.9, 1H), 6.82 (dt, J = 8.6, 3.1, 1H), 6.61 (d, J = 8.2, 1H), 5.64 (s, 1H), 5.52 (d, J = 14.0, 1H), 5.51 (s, 1H), 4.00 (s, 1H), 2.40 (m, 1H), 2.24 (s, 3H), 1.87 (m, 1H), 1.80 (m, 1H), 1.64 (m, 1H), 1.56 (s, 3H), 1.38 (s, 3H), 1.28 (m, 1H), 1.22 (m, 1H), 1.14 (s, 3H), 1.06 (m, 1H).

Compound **25** was isolated as a minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.2, 1H), 7.29 (dt, J = 9.4, 3.1, 1H), 6.86 (m, 1H), 6.82 (m, 1H), 6.61 (dd, J = 8.2,1.8, 1H), 5.63 (d, J = 10.1, 1H), 5.47 (s, 1H), 4.89 (s, 1H), 3.99 (s, 1H), 2.38 (m, 1H), 2.17 (s, 3H), 1.88 (m, 2H), 1.77 (m, 1H), 1.69 (m, 2H), 1.54 (s, 3H), 1.48 (m, 1H), 1.38 (d, J = 1.8, 3H), 1.20 (d, J = 1.2, 3H).

EXAMPLE 2

Preparation of (+)-*(5l,1'l)*-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (-)-*(5l,1'l)*-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **27** and **28**, Structure **3** of Scheme I, where $R^8 = R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^{10} = F$, $R^6 = R^{17} =$ methyl, R^{14}/R^{16} = a bond, n = 1)

These compounds were obtained through chiral HPLC separation of compound **24** using a Chiral AD Semiprep Column, 250x20 mm ID, 90% Hexanes/EtOH. Data for compound **27**, $[\alpha]^{22}_D = +332.3$ and compound **28**, $[\alpha]^{22}_D = -317.1$ (EtOH).

EXAMPLE 3

Preparation of (±)-*(5l,1'l)*-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (±)-*(5l,1'u)*-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **29** and **30**, Structure **3** of Scheme I, where $R^8 = R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, R^{10} = hydroxy, $R^6 = R^{17} =$ methyl, R^{14}/R^{16} = a bond, n = 1)

These compounds were prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)-3-methyl-1-cyclohexene (Structure **6** of Scheme I, where R^{17} = methyl, $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, n = 1) and 9-hydroxy-2,2,4-trimethyl-5-methoxy-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinoline (Compound **31**, Structure **2** of Scheme I, where $R^8 = R^9 = H$, R^{10} = hydroxy, R^6 = methyl).

Compound **29** was isolated as the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.2, 1H), 7.10 (d, J = 2.4, 1H), 6.86 (d, J = 8.5, 1H), 6.82 (dt, J = 8.6, 3.1, 1H), 6.62 (dd, J = 8.5, 2.7, 1H), 6.60 (d, J =8.2, 1H), 5.67 (s, 1H), 5.50 (s, 1H), 5.48 (d, J = 12.2, 1H), 3.96 (s, 1H), 2.42 (m, 1H), 2.24 (s, 3H), 1.87 (m, 1H), 1.77 (m, 1H), 1.66 (s, 3H), 1.64 (m, 1H), 1.38 (s, 3H), 1.28 (m, 1H), 1.20 (m, 1H), 1.13 (s, 3H), 1.02 (m, 1H).

Compound **30** was isolated as a minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.8, 1H), 7.18 (d, J = 3.7, 1H), 7.10 (d, J = 3.7, 1H), 6.81 (d, J = 7.9, 1H), 6.62 (m, 1H), 5.59 (d, J = 10.2, 1H), 5.47 (s, 1H), 4.90 (s, 1H), 4.45 (s, 1H), 3.96 (s, 1H), 2.40 (m, 1H), 2.17 (s, 3H), 1.88 (m, 1H), 1.78 (m, 1H), 1.68 (m, 1H), 1.60 (s, 3H), 1.38 (s, 3H), 1.30 (m, 2H), 1.20 (s, 3H), 0.90 (m, 1H).

EXAMPLE 4

Preparation of (+)-*(5l,1'l)*-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (-)-*(5l,1'l)*-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **32** and **33**, Structure **3** of Scheme I, where $R^8 = R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, R^{10} = hydroxy, $R^6 = R^{17}$ = methyl, R^{14}/R^{16} = a bond, n = 1)

These compounds were obtained through chiral HPLC separation of compound **29** using a Chiral AD Semiprep Column, 250x20 mm ID, 90% Hexanes/EtOH. Data for compound **32**, $[\alpha]^{22}_D$ = +201.6 and compound **33**, $[\alpha]^{22}_D$ = -207.7 (EtOH).

EXAMPLE 5

Preparation of (±)-*(5l,1'l)*-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline, (±)-*(5l,1'u)*-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **34** and **35**, Structure **3** of Scheme I, where $R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, $R^6 = R^{17}$ = methyl, R^{14}/R^{16} = a bond, n = 1) and (±)-5-(3-methylidene-cyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **87**, Structure **3** of Scheme I, where $R^9 = R^{13} = R^{14} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, R^6 = methyl, R^{16}/R^{17} = methylidene, n = 1)

These compounds were prepared in a similar fashion as that described in Example **1** general procedure from 3-dimethylphenylsilyl-3-methyl-1-cyclohexene (Structure **6** of Scheme I, where R^{17} = methyl, $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, n = 1) and 7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5-methoxy-5*H*-chromeno[3,4-*f*]quinoline (Compound **36**, Structure **5** of Scheme I, where $R^8 = R^{10}$ = fluorine, $R^9 = H$, R^6 = methyl).

Compound **34** was isolated as a major product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.36 (d, *J* = 8.2, 1H), 7.29 (dt, *J* = 9.4, 1.8, 1H), 6.70 (td, *J* = 9.5, 3.0, 1H), 6.61 (d, *J* = 8.2, 1H), 5.64 (d, *J* = 9.5, 1H), 5.63 (s, 1H), 5.51 (s, 1H), 4.04 (s, 1H), 2.38 (m, 1H), 2.24 (s, 3H), 1.88 (m, 1H), 1.77 (m, 1H), 1.69 (m, 1H), 1.65 (s, 3H), 1.39 (s, 3H), 1.30 (m, 1H), 1.25 (m, 1H), 1.14 (s, 3H), 1.10 (m, 1H).

Compound **35** was isolated as a miner product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.35 (d, *J* = 8.2, 1H), 7.10 (dt, *J* = 9.8, 2.4, 1H), 6.70 (td, *J* = 10.8, 3.0, 1H), 6.61 (d, *J* = 8.2, 1H), 5.74 (d, *J* = 10.4, 1H), 5.48 (s, 1H), 4.87 (s, 1H), 4.03 (s, 1H), 2.37 (m, 1H), 2.17 (s,

3H), 1.90 (m, 1H), 1.78 (m, 1H), 1.72 (m, 2H), 1.54 (s, 3H), 1.52 (m, 1H), 1.38 (s, 3H), 1.20 (d, J = 1.21, 3H).

Compound **87** was isolated as a 1.6:1 mixture of two diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) 7.36 (d, J = 8.2, 1H), 7.34 (d, J = 8.2, 1H), 7.14-7.08 (m, 2H), 6.73-6.67 (m, 2H), 6.60 (d, J = 11.3, 1H), 6.58 (d, J = 8.2, 1H), 6.10 (d, J = 10.1, 1H), 5.72 (d, J = 10.1, 1H), 5.64 (d, J = 9.2, 1H), 5.62 (s, 1H), 5.51 (s, 1H), 5.42 (s, 1H), 5.39-5.37 (m, 1H), 5.31-5.29 (m, 1H), 4.08-4.02 (m, 1H), 4.01-3.99 (m, 1H), 2.33-2.30 (m, 2H), 2.24 (s, 3H), 2.23 (s, 3H), 2.20-2.00 (m, 4H), 1.99-1.86 (m, 2H), 1.84-1.78 (m, 2H), 1.39 (s, 3H), 1.36 (s, 3H), 1.32-1.22 (m, 4H), 1.14 (s, 3H), 1.13 (s, 3H), 0.98-0.92 (m, 2H).

EXAMPLE 6

Preparation of (+)-*(5l,1'l)*-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (-)-*(5l,1'l)*-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **37** and **38**, Structure **3** of Scheme I, where $R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21}$ = H, $R^8 = R^{10}$ = fluorine, $R^6 = R^{17}$ = methyl, R^{14}/R^{16} = a bond, n = 1)

These compounds were obtained through chiral HPLC separation of compound **34** using a Chiral AD Semiprep Column, 250x20 mm ID, 90% Hexanes/EtOH. Data for compound **37**, $[\alpha]^{22}_D$ = +342.4 and compound **38**, $[\alpha]^{22}_D$ = -340.0 (EtOH).

EXAMPLE 7

Preparation of (±)-*(5l,1'l)*-5-(3-methyl-2-cyclohexenyl)-9-methoxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **39**, Structure **3** of Scheme I, where $R^8 = R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, R^{10} = methoxy, $R^6 = R^{17}$ = methyl, R^{14}/R^{16} = a bond, n = 1)

This compound was prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)-3-methyl-1-cyclohexene (Structure **6** of Scheme I, where R^{17} = methyl, $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, n =1) and 5,9-dimethoxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **40**, Structure **2** of Scheme I, where $R^8 = R^9 = H$, R^{10} = methoxy, R^6 = methyl) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) 7.43 (d, J = 7.9, 1H), 7.16 (s, 1H), 6.92 (d, J = 8.9, 1H), 6.72 (m, 1H), 6.62 (m, 1H), 5.59 (s, 1H), 5.49 (s, 1H), 5.48 (d, J = 9.8, 1H), 3.96 (s, 1H), 3.82 (s, 3H), 2.41 (m, 1H), 2.24 (s, 3H), 1.87 (m, 1H), 1.78 (m, 1H), 1.62 (m, 1H), 1.57 (s, 3H), 1.38 (s, 3H), 1.26 (m, 1H), 1.20 (m, 1H), 1.13 (s, 3H), 1.04 (m, 1H).

EXAMPLE 8

Preparation of (±)-*(5l,1'l)*-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinoline and (±)-*(5l,1'u)*-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **41** and **42**, Structure **3** of Scheme I, where $R^6 = R^8 = R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, R^{10} = fluorine, R^{17} = methyl, R^{14}/R^{16} = a bond, n = 1)

These compounds were prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)-3-methyl-1-cyclohexene (Structure **6** of Scheme I, where R^{17} = methyl, $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, n =1) and

9-fluoro-1,2-dihydro-2,2-dimethyl-5-methoxy-5*H*-chromeno[3,4-*f*]quinoline (Compound **43**, Structure **5** of Scheme I, where R^{10} = fluorine, $R^6 = R^8 = R^9 = H$).

Compound **41** was isolated as a major product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.5, 1H), 7.28 (dd, J = 9.8, 3.1, 1H), 6.89 (dd, J = 8.5, 4.9, 1H), 6.79 (dt, J = 8.6, 2.8, 1H), 6.48 (d, J = 8.5, 1H), 6.43 (d, J = 10.1, 1H), 5.62 (s, 1H), 5.58 (d, J = 10.1, 1H), 5.10 (d, J = 9.2, 1H), 3.86 (s, 1H), 2.44 (m, 1H), 1.89 (m, 1H), 1.80 (m, 1H), 1.74 (m, 1H), 1.56 (s, 3H), 1.35 (s, 3H), 1.34 (m, 2H), 1.31 (s, 3H), 1.27 (m, 1H).

Compound **42** was isolated as a minor product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.31 (d, J = 8.5, 1H), 7.28 (dd, J = 8.9, 2.1, 1H), 6.87 (dd, J = 9.2, 5.2, 1H), 6.80 (dt, J = 8.2, 3.1, 1H), 6.49 (d, J = 8.2, 1H), 6.36 (d, J = 10.1, 1H), 5.55 (d, J = 10.4, 1H), 5.10 (d, J = 10.1, 1H), 4.88 (s, 1H), 3.88 (s, 1H), 2.44 (m, 1H), 1.90 (m, 1H), 1.72 (m, 1H), 1.60 (m, 2H), 1.56 (s, 3H), 1.52 (m, 2H), 1.35 (s, 3H), 1.32 (s, 3H).

EXAMPLE 9

Preparation of (±)-*(5l,1'l)*-5-(3-methyl-2-cyclopentenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (±)-*(5l,1'u)*-5-(3-methyl-2-cyclopentenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **44** and **45**, Structure **3** of Scheme I, where $R^8 = R^9 = R^{13} = R^{15} = R^{19} = R^{20} = R^{21} = H$, $R^{10} = F$, $R^6 = R^{17}$ = methyl, R^{14}/R^{16} = a bond, n = 0)

These compounds were prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)-3-methylcyclopentene (Compound **46**, Structure **6** of Scheme I, where R^{17} = methyl, $R^{15} = R^{19} = R^{20} = R^{21} = H$,

n = 0) and compound **26** (Structure **2** of Scheme I, where $R^8 = R^9 = H$, R^{10} = fluorine, R^6 = methyl).

Compound **44** was isolated as a major product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.5, 1H), 7.29 (dd, J = 10.4, 2.8, 1H), 6.86 (dd, J = 8.9, 5.2, 1H), 6.79 (dt, J = 8.2, 3.1, 1H), 6.60 (d, J = 8.2, 1H), 5.61 (d, J = 8.8, 1H), 5.52 (s, 1H), 5.34 (s, 1H), 3.99 (s, 1H), 3.00 (m, 1H), 2.24 (s, 3H), 2.29 (m, 1H), 1.63 (m, 2H), 1.55 (s, 3H), 1.38 (s, 3H), 1.14 (s, 3H), 1.06 (m, 1H).

Compound **45** was isolated as a minor product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.2, 1H), 7.29 (dd, J = 8.8, 1.8, 1H), 6.85 (dd, J = 8.6, 5.2, 1H), 6.81 (dt, J = 8.2, 3.1, 1H), 6.60 (d, J = 8.2, 1H), 5.55 (d, J = 10.4, 1H), 5.47 (s, 1H), 4.81 (s, 1H), 3.99 (s, 1H), 2.96 (m, 1H), 2.34 (m, 1H), 2.18 (m, 1H), 2.14 (s, 3H), 2.09 (m, 1H), 1.91 (m, 1H), 1.55 (s, 3H), 1.38 (s, 3H), 1.20 (s, 3H).

EXAMPLE 10

Preparation of (±)-*(5l,1'l)*-5-(3,5,5-trimethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (±)-*(5l,1'u)*-5-(3,5,5-trimethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **47** and **48**, Structure **3** of Scheme I, where $R^8 = R^9 = R^{13} = R^{15} = R^{18} = R^{21} = H$, R^{10} = fluorine, $R^6 = R^{17} = R^{19} = R^{20}$ = methyl, R^{14}/R^{16} = a bond, n = 1)

These compounds were prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)-3,5,5-trimethylcyclohexene (Compound **49**, Structure **6** of Scheme I, where $R^{17} = R^{19} = R^{20}$ = methyl, $R^{15} = R^{18} = R^{21}$

= H, n = 1) and compound **26** (Structure **2** of Scheme I, where R^{10} = fluorine, R^6 = methyl, $R^8 = R^9 = H$).

Compound **47** was isolated as a major product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.39 (d, J = 8.2, 1H), 7.30 (dd, J = 9.8, 3.1, 1H), 6.91 (dd, J = 8.9, 4.9, 1H), 6.82 (dt, J = 8.6, 3.1, 1H), 6.62 (d, J = 8.2, 1H), 5.64 (s, 1H), 5.52 (d, J = 9.5, 1H), 5.51 (d, J = 1.2, 1H), 4.01 (s, 1H), 2.43 (m, 1H), 2.22 (d, J = 1.2, 3H), 1.77 (d, J = 17.1, 1H), 1.65 (s, 3H), 1.48 (d, J = 17.4, 1H), 1.38 (s, 3H), 1.12 (s, 3H), 0.88 (t, J = 12.2, 1H), 0.81 (s, 3H), 0.77 (m, 1H), 0.58 (s, 3H).

Compound **48** was isolated as a minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.2, 1H), 7.28 (dd, J = 10.1, 2.7, 1H), 6.87 (dd, J = 8.9, 5.2, 1H), 6.82 (dt, J = 7.9, 2.8, 1H), 6.62 (d, J = 8.2, 1H), 5.56 (d, J = 10.1, 1H), 5.50 (s, 1H), 4.94 (s, 1H), 3.99 (s, 1H), 2.42 (m, 1H), 2.17 (s, 3H), 1.83 (s, 1H), 1.56 (m, 4H), 1.38 (s, 3H), 1.22 (s, 3H), 0.97 (s, 3H), 0.58 (s, 3H).

EXAMPLE 11

Preparation of (±)-*(5l,1'l)*-5-(3-methyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline, (±)-*(5l,1'u)*-5-(3-methyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **50**, **51**, Structure **3** of Scheme I, where $R^9 = R^{13} = R^{15} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, $R^6 = R^{17}$ = methyl, R^{14}/R^{16} = a bond, n = 0) and (±)-5-(3-methyl-3-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **52**, Structure **3** of Scheme I, where $R^9 = R^{13} = R^{14} = R^{15} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, $R^6 = R^{17}$ = methyl, R^{16}/R^{19} = a bond, n = 0)

These compounds were prepared in a similar fashion as that described in Example **1** general procedure from compound **46** (Structure **6** of Scheme I, where R^{17} = methyl, $R^{15} = R^{19} = R^{20} = R^{21} = H$, n = 0) and compound **36** (Structure **2** of Scheme I, where $R^9 = H$, $R^8 = R^{10}$ = fluorine, R^6 = methyl).

Compound **50** was isolated as a major product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.35 (d, *J* = 8.2, 1H), 7.08 (d, *J* = 9.5, 1H), 6.68 (dt, *J* = 9.6, 2.8, 1H), 6.60 (d, *J* = 8.2, 1H), 5.73 (d, *J* = 8.5, 1H), 5.53 (s, 1H), 5.32 (s, 1H), 4.04 (s, 1H), 2.98 (m, 1H), 2.30 (m, 1H), 2.24 (s, 3H),2.12 (m, 1H), 1.66 (s, 3H), 1.65 (m, 1H), 1.38 (s, 3H), 1.14 (s, 3H), 0.88 (m, 1H).

Compound **51** was isolated as a minor product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.35 (d, *J* = 8.5, 1H), 7.09 (d, *J* = 7.9, 1H), 6.85 (t, 8.5, 1H), 6.60 (d, *J* = 8.2, 1H), 5.68 (d, *J* = 10.4, 1H), 5.48 (s, 1H), 4.79 (s, 1H), 3.99 (s, 1H), 2.95 (m, 1H), 2.36 (m, 1H), 2.18 (m, 1H), 2.14 (s, 3H), 1.94 (m, 1H), 1.65 (s, 3H), 1.38 (s, 3H), 1.20 (s, 3H), 0.88 (m, 1H).

Compound **52** was isolated as minor products: (*syn:anti* ratio of 2.2:1) ^{1}H NMR (500 MHz, $CDCl_3$) 7.33 (d, J = 8.6, 1H), 7.10 (dt, J = 9.8, 2.8, 1H), 6.69 (td, J = 9.5, 2.7, 1H), 6.61 (d, J = 8.2, 1H), 5.93 (d, J = 8.9, 1H), 5.53 (s, 1H), 5.41 (s, 1H), 4.03 (s, 1H), 2.88 (m, 1H), 2.23 (d, J = 0.6, 3H), 2.04 (m, 1H), 1.66 (s, 3H), 1.52 (m, 1H), 1.56 (m, 1H), 1.38 (s, 3H), 1.15 (s, 3H), 0.88 (m, 1H).

EXAMPLE 12

Preparation of (±)-5-(2-cyclopenta-1,3-dienyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **53**, Structure **3** of Scheme I, where $R^8 = R^9 = R^{15} = R^{17} = R^{20} = H$, R^{10} = fluorine, R^6 = methyl, R^{13}/R^{14} = a bond, R^{19}/R^{21} a bond, n = 0)

This compound was prepared in a similar fashion as that described in Example 1 general procedure from 5-(dimethylphenylsilyl)-1,3-cyclopentadiene (Compound **54**, Structure **6** of Scheme I, where $R^{15} = R^{17} = R^{20} = H$, R^{19}/R^{21} = a bond, n = 0) and compound **26** (Structure **2** of Scheme I, where R^{10} = fluorine, R^6 = methyl, $R^8 = R^9 = H$) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) 7.37 (d, J = 8.2, 1H), 7.23 (dd, J = 9.5, 2.8, 1H), 6.79 (dd, J = 8.6, 4.9, 1H), 6.74 (td, J = 8.4, 2.8, 1H), 6.64 (d, J = 8.2, 1H), 6.61 (s, 1H), 6.33 (dd, J = 5.2, 1.2, 1H), 6.22 (dt, J = 5.2, 1.8, 1H), 5.94 (t, J = 1.4, 1H), 5.48 (s, 1H), 3.94 (s, 1H), 3.08 (dd, J = 23.8, 1.5, 1H), 2.95 (dd, J = 23.8, 1.5, 1H), 2.11 (d, J = 1.5, 3H), 1.28 (s, 3H), 1.25 (s, 3H).

EXAMPLE 13

Preparation of (±)-*(5l,1'l)*-5-(3-ethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (±)-*(5l,1'u)*-5-(3-ethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **55** and **56**, Structure **3** of Scheme I, where $R^8 = R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, R^{10} = fluorine, R^6 = methyl, R^{17} = ethyl, R^{14}/R^{16} = a bond, n = 1)

These compounds were prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)-3-ethylcyclohexene (Compound **57**, Structure **6** of Scheme I, where R^{17} = ethyl, $R^{15} = R^{18} = R^{19} = R^{20} = R^{21}$ = H, n = 1) and compound **26** (Structure **2** of Scheme I, where R^{10} = fluorine, R^6 = methyl, $R^8 = R^9$ = H).

Compound **55** was isolated as a major product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, *J* = 8.2, 1H), 7.29 (dd, *J* = 9.8, 3.1, 1H), 6.90 (dd, *J* = 8.9, 4.9, 1H), 6.81 (dt, *J* = 8.2, 2.8, 1H), 6.61 (d, *J* = 8.2, 1H), 5.59 (s, 1H), 5.56 (d, *J* = 9.5, 1H), 5.50 (d, *J* = 0.9, 1H), 4.00 (s, 1H), 2.40 (m, 1H), 2.24 (d, *J* = 0.9, 3H), 1.93 (q, *J* = 6.7, 2H), 1.88 (m, 1H), 1.80 (m, 1H), 1.67 (m, 1H), 1.38 (s, 3H), 1.27 (m, 1H), 1.22 (m, 1H), 1.14 (s, 3H), 0.98 (m, 1H), 0.95 (t, *J* = 7.6, 3H).

Compound **56** was isolated as a minor product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, *J* = 7.9, 1H), 7.29 (dd, *J* = 9.8, 3.1, 1H), 6.86 (m, 1H), 6.82 (m, 1H), 6.61 (d, *J* = 8.2, 1H), 5.59 (d, *J* = 10.7, 1H), 5.46 (s, 1H), 4.92 (s, 1H), 3.98 (s, 1H), 2.40 (m, 1H), 2.18 (s, 3H), 1.98 (m, 1H), 1.85 (q, *J* = 7.9, 2H), 1.70 (m, 3H), 1.46 (m, 1H), 1.38 (s, 3H), 1.20 (s, 3H), 0.98 (m, 1H), 0.94 (t, *J* = 7.6, 3H).

EXAMPLE 14

Preparation of (±)-*(5l,1'l)*-5-(3-methyl-2-cyclohexenyl)-7-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (±)-*(5l,1'u)*-5-(3-methyl-2-cyclohexenyl)-7-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **58** and **59**, Structure **3** of Scheme I, where $R^9 = R^{10} = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, R^8 = fluorine, $R^6 = R^{17}$ = methyl, R^{14}/R^{16} = a bond, n = 1)

These compounds were prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)-3-methyl-1-cyclohexene (Structure **6** of Scheme I, where R^{17} = methyl, $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, n = 1) and 7-fluoro-1,2-dihydro-2,2,4-trimethyl-5-methoxy-5*H*-chromeno[3,4-*f*]quinoline (Compound **60**, Structure **2** of Scheme I, where R^8 = fluorine, R^6 = methyl, $R^9 = R^{10} = H$).

Compound **58** was isolated as a major product: ^{1}H NMR (500 MHz, acetone-d_6) 7.54 (d, J = 8.2, 1H), 7.50 (d, J = 7.6, 1H), 6.95 (m, 2H), 6.75 (d, J = 8.2, 1H), 5.64 (s, 1H), 5.63 (s, 1H), 5.62 (d, J = 9.5, 1H), 5.54 (s, 1H), 2.36 (m, 1H), 2.23 (s, 3H), 1.90 (m, 1H), 1.78 (m, 1H), 1.70 (m, 1H), 1.62 (s, 3H), 1.37 (s, 3H), 1.29 (m, 2H), 1.13 (s, 3H).

Compound **59** was isolated as a minor product: ^{1}H NMR (500 MHz, acetone-d_6) 7.53 (d, J = 8.5, 1H), 7.50 (d, J = 6.7, 1H), 6.96 (m, 2H), 6.76 (d, J = 8.2, 1H), 5.73 (d, J = 10.4, 1H), 5.64 (s, 1H, 5.51 (d, J = 1.2, 1H), 4.96 (m, 1H), 2.35 (m, 1H), 2.18 (s, 3H), 1.90 (m, 1H), 1.80 (m, 1H), 1.73 (m, 1H), 1.58 (s, 3H), 1.48 (m, 1H), 1.37 (s, 3H), 1.28 (m, 1H), 1.21 (s, 3H).

EXAMPLE 15

Preparation of (±)-*(5l,1'l)*-5-(3-ethyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **61**, Structure **3** of Scheme where $R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, R^6 = methyl, R^{17} = ethyl, R^{14}/R^{16} = a bond, n = 1), (±)-*(5l,1'l)*-5-(3-ethylidenecyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **62**, Structure **3** of Scheme where $R^9 = R^{13} = R^{14} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, R^6 = methyl, R^{16}/R^{17} = ethylidene, n = 1) and (±)-*(5l,1'u)*-5-(3-ethylidenecyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **88**, Structure **3** of Scheme where $R^9 = R^{13} = R^{14} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, R^6 = methyl, R^{16}/R^{17} = ethylidene, n = 1)

These compounds were prepared in a similar fashion as that described in Example **1** general procedure from compound **57** (Structure **6** of Scheme I, where R^{17} = ethyl, $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, n = 1) and compound **36** (Structure **5** of Scheme II, where $R^8 = R^{10}$ = fluorine, R^6 = methyl, $R^9 = H$).

Compound **61** was isolated as a major product: ^{1}H NMR (500 MHz, CD_3COCD_3) 7.54 (d, *J* = 8.2, 1H), 7.31 (dt, *J* = 8.9, 1.8, 1H), 6.83 (td, 9.4, 3.0, 1H), 6.76 (d, *J* = 8.2, 1H), 5.72 (m, 2H), 5.55 (d, *J* = 4.9, 1H), 5.53 (s, 1H), 2.80 (s, 3H), 2.36 (m, 1H), 2.22 (s, 3H), 1.90 (q, *J* = 7.6, 2H), 1.82 (m, 1H), 1.72 (m, 1H), 1.30 (m, 1H), 1.37 (s, 3H), 1.14 (s, 3H), 0.90 (t, *J* = 7.6, 3H).

Compound **62** was isolated as a minor product: ^{1}H NMR (500 MHz, CD_3COCD_3) 7.51 (d, *J* = 8.2, 1H), 7.30 (dt, *J* = 10.1, 2.8, 1H), 6.83 (td, 9.6, 2.8, 1H), 6.75 (d, *J* = 8.6, 1H), 5.87 (d, *J* = 10.1, 1H), 5.71 (s, 1H), 5.57 (d, *J* = 1.5, 1H), 5.03 (m, 1H), 2.84 (s, 3H),

2.39 (m, 1H), 2.16 (m, 1H), 2.22 (m, 1H), 1.90 (m, 2H), 1.82 (m, 1H), 1.70 (m, 1H), 1.60 (m, 1H), 1.50 (m, 1H), 1.38 (s, 3H), 1.14 (s, 3H), 0.83 (d, J = 7.3, 3H).

Compound **88** was isolated as a 1:1 mixture of two E/Z-isomers: ^{1}H NMR (500 MHz, acetone-d_6) 7.50 (d, J = 8.5, 1H), 7.49 (d, J = 8.5, 1H), 7.34-7.24 (m, 2H), 6.90-6.80 (m, 2H), 6.64 (d, J = 8.5, 1H), 6.61 (d, J = 8.5, 1H), 5.86 (d, J = 7.9, 1H), 5.80 (d, J = 7.9, 1H), 5.49 (s, 1H), 5.36 (s, 1H), 5.34 (s, 1H), 5.22 (s, 1H), 5.16 (s, 1H), 4.79 (s, 1H), 2.44-2.38 (m, 1H), 2.34-2.28 (m, 1H), 2.25 (s, 3H), 2.23 (s, 3H), 1.90-1.74 (m, 6H), 1.68-1.58 (m, 2H), 1.34 (s, 3H), 1.30 (s, 3H), 1.36-1.22 (m, 8H), 1.22 (s, 3H), 1.18 (s, 3H), 0.92-0.84 (m, 6H).

EXAMPLE 16

Preparation of (±)-*(5l,1'l)*-5-(3-methyl-3-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **63**, Structure **3** of Scheme I, where $R^9 = R^{13} = R^{14} = R^{15} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, $R^6 = R^{17}$ = methyl, R^{16}/R^{18} = a bond, n = 1)

This compound was isolated as a minor product after treatment of compound **34** (Structure **3** of Scheme I, where $R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, $R^6 = R^{17}$ = methyl, R^{14}/R^{16} = a bond, n = 1) with acid: ^{1}H NMR (500 MHz, $CDCl_3$) 7.33 (d, J = 8.5, 1H), 7.10 (d, J = 10.1, 1H), 6.70 (td, J = 10.4, 2.4, 1H), 6.60 (d, J = 8.5, 1H), 6.01 (d, J = 7.9, 1H), 5.51 (s, 1H), 5.47 (s, 1H), 4.04 (s, 1H), 2.41 (m, 1H), 2.24 (s, 3H), 1.95 (m, 2H), 1.86 (s, 3H), 1.52 (m, 1H), 1.38 (s, 3H), 1.18 (m, 1H), 1.14 (s, 3H), 1.12 (m, 1H), 0.97 (m, 1H).

EXAMPLE 17

Preparation of (±)-*(5l,1'l)*-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-8-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (±)-*(5l,1'u)*-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-8-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **64** and **65**, Structure **3** of Scheme I, where $R^8 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, R^9 = methoxy, $R^6 = R^{17}$ = methyl, R^{10} = fluorine, R^{14}/R^{16} = a bond, n = 1)

These compounds were prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)-3-methyl-1-cyclohexene (Structure **6** of Scheme I, where R^{17} = methyl, $R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, n = 1) and 9-fluoro-1,2-dihydro-5,8-dimethoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **66**, Structure **2** of Scheme I, where $R^8 = H$, R^6 = methyl, R^9 = methoxy, R^{10} = fluorine).

Compound **64** was isolated as a major product: ^{1}H NMR (500 MHz, CD_3COCD_3) 7.44 (d, *J* =12.5, 1H), 7.42 (d, *J* = 8.2, 1H), 6.73 (d, *J* = 6.6, 1H), 6.71 (d, *J* = 7.2, 1H), 5.68 (s, 1H), 5.52 (m, 2H), 5.48 (s, 1H), 3.90 (s, 3H), 2.40 (m, 1H), 2.20 (s, 3H), 2.08 (m, 1H), 1.96 (m, 1H), 1.78 (m, 1H), 1.65 (m, 1H), 1.63 (s, 3H), 1.36 (s, 3H), 1.26 (m, 2H), 1.12 (s, 3H).

Compound **65** was isolated as a minor product: ^{1}H NMR (500 MHz, CD_3COCD_3) 7.44 (d, *J* =12.5, 1H), 7.42 (d, *J* = 8.2, 1H), 6.73 (d, *J* = 8.2, 1H), 6.70 (d, *J* = 7.6, 1H), 5.63 (s, 1H), 5.48 (s, 1H), 5.46 (d, *J* = 12.5, 1H), 4.96 (m, 1H), 3.88 (s, 3H), 2.39 (m, 1H), 2.20 (s, 3H), 1.94 (m, 1H), 1.78 (m, 1H), 1.72 (m, 1H), 1.57 (s, 3H), 1.46 (m, 1H), 1.36 (s, 3H), 1.28 (m, 2H), 1.20 (s, 3H).

EXAMPLE 18

Preparation of (±)-*(5l,1'l)*-5-(2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline, (±)-*(5l,1'u)*-5-(2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **67**, **68**, Structure **3** of Scheme I, where $R^9 = R^{13} = R^{15} = R^{17} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, R^6 = methyl, R^{14}/R^{16} = a bond, n = 0) and (±)-5-(1-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **69**, Structure **3** of Scheme I, where $R^9 = R^{15} = R^{16} = R^{17} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, R^6 = methyl, R^{13}/R^{14} = a bond, n = 0)

These compounds were prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)cyclopentene (Compound **70**, Structure **6** of Scheme I, where $R^{15} = R^{17} = R^{19} = R^{20} = R^{21} = H$, n = 0) and compound **36** (Structure **2** of Scheme I, where $R^8 = R^{10}$ = fluorine, R^6 = methyl, $R^9 = H$).

Compound **61** was isolated as a major product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.37 (d, J = 8.2, 1H), 7.10 (dt, J = 9.5, 2.7, 1H), 6.71 (td, J = 9.5, 3.1, 1H), 6.61 (d, J = 8.2, 1H), 5.77 (ddd, 1H), 5.71 (d, J = 10.4, 1H), 5.48 (d, J = 1.2, 1H), 5.23 (ddd, 1H), 5.53 (s, 1H), 4.02 (s, 1H), 3.01 (m, 1H), 2.46 (m, 1H), 2.28 (m, 1H), 2.07 (m, 1H), 1.95 (m, 1H), 1.39 (s, 3H), 1.28 (m, 2H), 1.19 (s, 3H).

Compound **62** was isolated as a minor product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.37 (d, J = 8.2, 1H), 7.09 (dt, J = 9.8, 1.8, 1H), 6.69 (td, J = 9.6, 2.8, 1H), 6.61 (d, J = 8.6, 1H), 5.78 (m, 1H), 5.77 (s, 1H), 5.75 (s, 1H), 5.74 (m, 1H), 5.53 (s, 1H), 4.05 (s, 1H), 2.93 (m, 1H), 2.38 (m, 1H), 2.24 (d, J =0.9, 3H), 1.63 (m, 2H), 1.39 (s, 3H), 1.15 (s, 3H).

Compound **63** was isolated as a minor product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.31 (d, J = 8.6, 1H), 7.04 (m, 1H), 6.66 (m, 1H), 6.61 (d, J = 8.6, 1H), 6.31 (m, 1H), 5.49 (m, 1H), 5.16 (q, J = 1.8, 1H), 3.96 (s, 1H), 2.52 (m, 1H), 2.35 (m, 1H), 2.18 (s, 3H), 1.85 (m, 1H), 1.78 (m, 1H), 1.29 (d, J = 20.8, 3H), 1.16 (m, 2H), 1.15 (s, 3H).

EXAMPLE 19

Preparation of (±)-*(5l,1'l)*-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **71**, Structure **3** of Scheme I, where $R^9 = R^{13} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, $R^6 = R^{15} = R^{17}$ = methyl, R^{14}/R^{16} = a bond, n = 0)

This compound was prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)-2,3-dimethylcyclopentene (Compound **72**, Structure **6** of Scheme I, where $R^{19} = R^{20} = R^{21} = H$, $R^{15} = R^{17}$ = methyl, n = 0) and compound **36** (Structure **2** of Scheme I, where $R^8 = R^{10}$ = fluorine, R^6 = methyl, $R^9 = H$) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) 7.32 (d, J = 8.2, 1H), 7.09 (dt, J = 9.8, 2.7, 1H), 6.69 (td, J = 10.8, 2.8, 1H), 6.59 (d, J = 7.5, 1H), 5.92 (d, J = 8.2, 1H), 5.53 (s, 1H), 4.01 (s, 1H), 2.86 (m, 1H), 2.29 (m, 1H), 2.22 (s, 3H), 2.00 (m, 1H), 1.57 (s, 3H), 1.55 (s, 3H), 1.50 (m, 1H), 1.38 (s, 3H), 1.14 (s, 3H).

EXAMPLE 20

Preparation of (+)-*(5l,1'l)*-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (-)-*(5l,1'l)*-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **73** and **74**, Structure **3** of Scheme I, where $R^9 = R^{13} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, $R^6 = R^{15} = R^{17}$ = methyl, R^{14}/R^{16} = a bond, n = 0)

These compounds were obtained through chiral HPLC separation of compound **71** using a Chiral AD Semiprep Column, 250x20 mm ID, 90% Hexanes/EtOH. Data for compound **73**, $[\alpha]^{22}_D = +256.7$ and compound **74**, $[\alpha]^{22}_D = -263.8$ (EtOH).

EXAMPLE 21

Preparation of (±)-*(5l,1'l)*-5-(2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline, (±)-*(5l,1'u)*-5-(2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **75** and **76**, Structure **3** of Scheme I, where $R^9 = R^{15} = R^{16} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, R^6 = methyl, R^{13}/R^{14} = a bond, n = 1) and (±)-*(5l,1'l)*-5-(2-cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-5*H*-chromeno[3,4-*f*]quinoline (Compound **77**, Structure **4** of Scheme I, where $R^4 = R^{17} = H$, X = O)

These compounds were prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)cyclohexene (Compound **78**, Structure **6** of Scheme I, where $R^{15} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21} = H$, n = 1) and compound **36** (Structure **2** of Scheme I, where $R^8 = R^{10}$ = fluorine, R^6 = methyl, $R^9 = H$).

Compound **75** was isolated as a major product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.35 (d, J = 8.2, 1H), 7.08 (td, J = 9.8, 1.8, 1H), 6.69 (dt, J = 9.5, 3.0, 1H), 6.61 (d, J = 8.2, 1H), 5.90 (d, J = 11.0, 1H), 5.76 (m, 1H), 5.68 (d, J = 9.5, 1H), 5.52 (d, J = 1.2, 1H), 4.06 (s, 1H), 2.41 (m, 1H), 2.24 (d, J = 1, 3H), 1.94 (m, 2H), 1.66 (m, 2H), 1.39 (s, 3H), 1.28 (m, 1H), 1.25 (m, 1H), 1.14 (s, 3H).

Compound **76** was isolated as a minor product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.35 (d, J = 8.2, 1H), 7.10 (td, J = 9.8, 1.8, 1H), 6.70 (dt, J = 8.6, 2.7, 1H), 6.60 (d, J = 8.2, 1H), 5.78 (d, J = 10.4, 1H), 5.68 (m, 1H), 5.48 (s, 1H), 5.12 (d, J = 7.9, 1H), 4.04 (s, 1H), 2.41 (m, 1H), 2.20 (s, 3H), 1.98 (m, 2H), 1.78 (m, 2H), 1.38 (s, 3H), 1.28 (m, 1H), 1.25 (m, 1H), 1.18 (s, 3H).

Compound **77** was isolated as a minor product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.31 (d, J = 8.6, 1H), 7.08 (m, 1H), 6.68 (m, 1H), 6.43 (d, J = 8.2, 1H), 5.85 (m, 1H), 5.73 (m, 1H), 5.40 (s, 1H), 5.18 (s, 1H), 4.04 (s, 1H), 2.33 (d, J = 11.3, 1H), 2.27 (d, J = 12.2, 1H), 2.00 (m, 1H), 1.93 (m, 1H), 1.68 (m, 1H), 1.94 (m, 2H), 1.34 (s, 3H), 1.18 (m, 1H), 1.14 (s, 3H), 0.86 (m, 2H).

EXAMPLE 22

Preparation of (±)-*(5l,1'l)*-5-(2-methylidenecyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (±)-*(5l,1'u)*-5-(2-methylidenecyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **79** and **80**, Structure **3** of Scheme I, where $R^8 = R^9 = R^{13} = R^{16} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21} = H$, R^{10} = fluorine, R^6 = methyl, R^{14}/R^{15} = methylidene, n = 1)

(±)-*(5l,1'l)*-5-(2-oxocyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline and (±)-*(5l,1'u)*-5-(2-oxocyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **81** and **82**, Structure **3** of Scheme I, where $R^8 = R^9 = R^{13} = R^{16} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21} = H$, R^{10} = fluorine, R^6 = methyl, R^{14}/R^{15} = carbonyl, n = 1)

Compounds **81** and **82** were prepared in a similar fashion as that described in Example **1** general procedure from 1-(trimethylsilyloxy)cyclohexene and compound **26** (Structure **2** of Scheme I, where R^{10} = fluorine, R^6 = methyl, $R^8 = R^9 = H$).

Compound **81** was isolated as a major product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.36 (d, J = 8.6, 1H), 7.30 (dd, J = 13.4, 4.6, 1H), 6.81 (d, J = 7.0, 1H), 6.80 (d, J = 8.2, 1H), 6.61 (d, J = 8.5, 1H), 6.58 (d, J = 9.2, 1H), 5.49 (s, 1H), 3.99 (s, 1H), 2.84 (m, 1H), 2.45 (m, 1H), 2.28 (s, 3H), 2.24 (m, 1H), 1.99 (m, 1H), 1.68 (m, 2H), 1.40 (m, 2H), 1.37 (s, 3H), 1.11 (s, 3H).

Compound **82** was isolated as a minor product: ^{1}H NMR (500 MHz, $CDCl_3$) 7.36 (d, J = 8.6, 1H), 7.30 (dd, J = 7.3, 1H), 6.81 (d, J = 8.8, 1H), 6.79 (d, J = 7.6, 1H), 6.59

(d, J = 8.2, 1H), 6.44 (d, J = 5.8, 1H), 5.49 (s, 1H), 3.99 (s, 1H), 2.59 (m, 1H), 2.35 (m, 1H), 2.26 (s, 3H), 2.20 (m, 1H), 1.90 (m, 2H), 1.80 (m, 1H), 1.70 (m, 2H), 1.45 (m, 2H), 1.37 (s, 3H), 1.12 (s, 3H).

The title compounds **79** and **80** were prepared by using a Wittig procedure from compounds **81** and **82**. Data for compound **79**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.2, 1H), 7.31 (dd, J = 7.6, 2.8, 1H), 6.78 (m, 1H), 6.80 (d, J = 8.2, 1H), 6.61 (m, 1H), 6.02 (d, J = 10.1, 1H), 5.52 (s, 1H), 4.83 (s, 1H), 4.71 (s, 1H), 4.02 (s, 1H), 2.50 (m, 1H), 2.42 (s, 3H), 2.30 (m, 1H), 2.07 (m, 1H), 1.60 m, m1H), 1.45 (m, 2H), 1.39 (s, 3H), 1.30 (m, 1H), 1.18 (m, 1H), 1.12 (s, 3H, 1.08 (m, 1H). Data for compound **80**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.8, 1H), 7.34 (m, 1H), 6.78 (m, 1H), 6.86 (m, 1H), 6.54 (d, J = 8.9, 1H), 6.01 (d, J = 9.2, 1H), 5.47 (s, 1H), 4.41 (s, 1H), 4.10 (s, 1H), 3.98 (s, 1H), 2.56 (m, 1H), 2.30 (s, 3H), 2.04 (m, 3H), 1.76 (m, 1H), 1.68 (m, 1H), 1.58 (m, 1H), 1.36 (s, 3H), 1.30 (m, 2H), 1.09 (s, 3H).

EXAMPLE 23

Preparation of (±)-*(5l,1'l)*-5-(3-methyl-2-cyclohexenyl)-9-methoxy-1,2-dihydro-1,2,2,4-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **83**, Structure **5** of Scheme I)

This compound was prepared by methylation of compound **39** (Structure **3** of Scheme I, where $R^8 = R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, R^{10} = methoxy, $R^6 = R^{17}$ = methyl, R^{14}/R^{16} = a bond, n = 1) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) 7.56 (d, J = 8.5, 1H), 7.28 (d, J = 2.1, 1H), 6.92 (d, J = 8.9, 1H), 6.75 (m, 2H), 5.69 (s, 1H), 5.54 (s, 1H), 5.50 (d, J = 9.8, 1H), 3.83 (s, 3H), 2.89 (s, 3 H), 2.41 (m, 1H), 2.26 (s,

3H), 1.87 (m, 1H), 1.77 (m, 1H), 1.66 (s, 3H), 1.62 (m, 1H), 1.51 (s, 3H), 1.28 (m, 2H), 1.18 (m, 1H), 0.96 (s, 3H).

EXAMPLE 24

Preparation of (±)-5-(2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compounds **84**, Structure **3** of Scheme I, where $R^8 = R^9 = R^{13} = R^{15} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^{10} = F$, R^6 = methyl, R^{14}/R^{16} = a bond, n = 1)

This compound was prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)cyclohexene (Compound **78**, Structure **6** of Scheme I, where $R^{15} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21} = H$, n = 1) and compound **26** (Structure **2** of Scheme I, where R^{10} = fluorine, R^6 = methyl, $R^8 = R^9 = H$) as a 1:1 mixture of two diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38 (d, J = 8.2, 1H), 7.38 (d, J = 8.2, 1H), 7.30 (t, J = 2.8, 1H), 7.28 (t, J = 2.8, 1H), 6.90-6.85 (m, 2H), 6.85-6.80 (m, 2H), 6.61 (d, J = 8.2, 1H), 6.61 (d, J = 8.2, 1H), 5.91 (d, J = 10.1, 1H), 5.78-5.71 (m, 1H), 5.67 (d, J = 10.1, 1H), 5.70-5.64 (m, 1H), 5.57 (d, J = 9.8, 1H), 5.51 (s, 1H), 5.47 (s, 1H), 5.18-5.14 (m, 1H), 4.02-3.98 (m, 2H), 2.46-2.38 (m, 1H), 2.24 (s, 3H), 2.20 (s, 3H), 2.04-1.90 (m, 4H), 1.80-1.70 (m, 3H), 1.68-1.62 (m, 1H), 1.48-1.42 (m, 1H), 1.49 (s, 3H), 1.47 (s, 3H), 1.32-1.22 (m, 2H), 1.16 (s, 3H), 1.14 (s, 3H), 0.98-0.92 (m, 2H).

EXAMPLE 25

Preparation of (±)-*(5l,1'l)*-5-(2,3-dimethyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **85**, Structure **3** of Scheme I, where $R^9 = R^{13} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, $R^6 = R^{15} = R^{17}$ = methyl, R^{14}/R^{16} = a bond, n = 1)

This compound was prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)-2,3-dimethylcyclohexene (Compound **86**, Structure **6** of Scheme I, where $R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^{15} = R^{17}$ = methyl, n = 1) and Compound **36** (Structure **2** of Scheme I, where $R^8 = R^{10}$ = fluorine, $R^9 = H$, R^6 = methyl) as a yellow solid: ^{1}H NMR (500 MHz, acetone-d_6) 7.50 (d, J = 8.2, 1H), 7.30 (dt, J = 10.1, 1.8, 1H), 6.84 (td, J = 9.8, 2.8, 1H), 6.75 (d, J = 8.2, 1H), 6.01 (d, J = 6.4, 1H), 5.72 (s, 1H), 5.55 (d, 1.2, 1H), 2.30 (m, 1H), 2.22 (s, 3H), 2.00-1.8 (m, 3H), 1.59 (s, 3H), 1.50 (s, 3H), 1.46-1.40 (m, 1H), 1.37 (s, 3H), 1.36-1.26 (m, 3H), 1.15 (s, 3H).

EXAMPLE 26

Preparation of (±)-*(5l,1'l)*- 5-(2-cycloheptenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound **89**, Structure **3** of Scheme I, where $R^9 = R^{13} = R^{15} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, R^6 = methyl, R^{14}/R^{16} = a bond, n = 2)

This compound was prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)cycloheptene (Compound **90**, Structure **6** of Scheme I, where $R^{15} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21} = H$, n = 2) and Compound **36** (Structure **2** of Scheme I, where $R^8 = R^{10}$ = fluorine, $R^9 = H$, R^6 = methyl) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) 7.36 (d, J = 8.6, 1H), 7.10 (d, J = 9.8, 1H), 6.68 (ddd,

J = 9.5, 2.8, 2.8, 1H), 6.61 (d, J = 8.2, 1H), 6.03 (d, J = 11.6, 1H), 5.84-5.76 (m, 1H), 5.80 (d, J = 10.1, 1H), 5.52 (s, 1H), 4.10 (s, 1H), 2.47 (m, 1H), 2.24 (s, 3H), 2.12-2.04 (m, 2H), 1.94-1.84 (m, 1H), 1.78-1.84 (m, 1H), 1.44-1.44 (m, 1H), 1.38 (s, 3H), 1.24-1.18 (m, 2H), 1.11 (s, 3H), 0.98-0.92 (m, 1H).

EXAMPLE 27

Preparation of (±)-*(5l,1'l)*- 5-(2-cyclooctenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline and (±)-*(5l,1'u)*- 5-(2-cyclooctenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compounds **91** and **92**, Structure **3** of Scheme I, where $R^9 = R^{13} = R^{15} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21}$ = H, $R^8 = R^{10}$ = fluorine, R^6 = methyl, R^{14}/R^{16} = a bond, n = 3)

These compounds were prepared in a similar fashion as that described in Example **1** general procedure from 3-(dimethylphenylsilyl)cyclooctene (Compound **93**, Structure **6** of Scheme I, where $R^{13} = R^{15} = R^{17} = R^{18} = R^{19} = R^{20} = R^{21}$ =H, n = 3) and Compound **36** (Structure **2** of Scheme I, where $R^8 = R^{10}$ = fluorine, R^9 = H, R^6 = methyl) as a yellow solid: Compound **91** ^{1}H NMR (500 MHz, $CDCl_3$) 7.36 (d, J = 8.6, 1H), 7.10 (d, J = 9.8, 1H), 6.68 (ddd, J = 9.5, 2.8, 2.8, 1H), 6.58 (d, J = 8.2, 1H), 5.87 (d, J = 9.5, 1H), 5.74-5.66 (m, 1H), 5.56 (t, J = 10.1, 1H), 5.52 (s, 1H), 4.03 (s, 1H), 2.90-2.80 (m, 1H), 2.26 (s, 3H), 1.88-1.80 (m, 1H), 1.54-1.46 (m, 2H), 1.40-1.32 (m, 2H), 1.23-1.17 (m, 2H), 1.38 (s, 3H), 1.24-1.18 (m, 2H), 1.19 (s, 3H), 1.07-0.98 (m, 1H); Compound **92** ^{1}H NMR (500 MHz, $CDCl_3$) 7.33 (d, J = 8.5, 1H), 7.11 (d, J = 9.8, 1H), 6.71 (ddd, J = 9.5, 2.8, 2.8, 1H), 6.61 (d, J = 8.2, 1H), 5.87 (d, J = 8.8, 1H), 5.54 (s, 1H), 5.54-5.48 (m, 1H), 5.23 (t, J = 10.4, 1H), 4.01 (s, 1H), 2.88-2.80 (m, 1H), 2.26 (s, 3H), 1.96-1.88 (m,

1H), 1.84-1.70 (m, 2H), 1.54-1.46 (m, 2H), 1.45-1.38 (m, 1H), 1.38 (s, 3H), 1.36-1.26-1.17 (m, 2H), 1.20-1.00 (m, 2H), 1.10 (s, 3H).

EXAMPLE 28

Preparation of (±)-*(5l,1'l)*- 5-(2,3-epoxy-3-methylcyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound **94**, Structure **3** of Scheme I, where $R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, $R^6 = R^{17}$ = methyl, R^{14}/R^{16} = -O-, n = 1) and (±)-*(5l,1'l)*- 5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro- 2,2-dimethyl-4-methylene-5*H*-chromeno[3,4-f]quinolin-3-ol (Compound **95**, Structure **4** of Scheme I, where R^4 = hydroxy, R^{17} = methyl, X = O)

These compounds were prepared by epoxidation of Compound **34** (Structure **3** of Scheme I, where $R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, $R^6 = R^{17}$ = methyl, R^{14}/R^{16} = a bond, n = 1) according to a standard procedure as yellow solids: Compound **94**, ^{1}H NMR (500 MHz, acetone-d_6) 7.54 (d, J = 8.5, 1H), 7.35 (ddd, J = 9.2,1.8, 1.8, 1H), 6.89 (ddd, J = 9.5, 2.8, 2.8, 1H), 6.76 (d, J = 8.5, 1H), 6.02 (d, J = 10.1, 1H), 5.74 (s, 1H), 5.54 (s, 1H), 3.15 (d, J = 2.1, 1H), 2.28 (d, J = 0.6, 3H), 2.16-2.00 (m, 1H), 1.72-1.66 (m, 2H), 1.37 (s, 3H), 1.40-1.28 (m, 1H), 1.28 (s, 3H), 1.11 (s, 3H), 1.08-0.93 (m, 2H), 0.84-0.76 (m, 1H; Compound **95**, ^{1}H NMR (500 MHz, acetone-d_6) 7.48 (d, J = 8.5, 1H), 7.28 (ddd, J = 9.2,1.8, 1.8, 1H), 6.83 (ddd, J = 9.5, 2.8, 2.8, 1H), 6.60 (d, J = 8.5, 1H), 5.80 (d, J = 8.8, 1H),.5.70 (d, J = 21.4, 1H), 5.68 (s, 1H), 5.55 (s, 1H), 5.41 (s, 1H), 4.55 (d, J = 4.9, 1H), 4.18 (dt, J = 4.6, 1.2, 1H), 2.30-2.22 (m, 1H), 1.90-1.74 (m, 1H), 1.74-1.66 (m, 1H), 1.58 (s, 3H), 1.35 (s, 3H), 1.32-1.24 (m, 4H), 1.08 (s, 3H).

EXAMPLE 29

Preparation of (±)-*(5l,1'l)*- 5-(2,3-epoxy-2,3-dimethylcyclopentyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound **96**, Structure **3** of Scheme I, where $R^9 = R^{13} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, $R^6 = R^{15} = R^{17}$ = methyl, R^{14}/R^{15} = -O-, n = 0)

This compound was prepared by epoxidation of Compound **71** (Structure **3** of Scheme I, where $R^9 = R^{13} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, $R^6 = R^{15} = R^{17}$ = methyl, R^{14}/R^{16} = a bond, n = 0) as a solid: ^{1}H NMR (500 MHz, acetone-d_6) 7.49 (d, J = 8.5, 1H), 7.34 (ddd, J = 9.2,1.8, 1.8, 1H), 6.89 (ddd, J = 9.5, 2.8, 2.8, 1H), 6.73 (d, J = 8.6, 1H), 6.18 (d, J = 9.5, 1H), 5.68 (s, 1H), 5.53 (s, 1H), 2.35 (dt, J = 9.8, 1.8, 1H), 2.28 (d, J = 0.6, 3H), 1.69 (dd, J = 13.7, 8.2, 1H), 1.48 (s, 3H), 1.47-1.43 (m, 1H), 1.36 (s, 3H), 1.25 (s, 3H), 1.01 (s, 3H), 0.98-0.92 (m, 1H), 0.78-0.72 (m, 1H).

EXAMPLE 30

Preparation of (±)-*(5l,1'u)*- 5-(2,3-epoxy-3-methylcyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound **97**, Structure **3** of Scheme I, where $R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, $R^6 = R^{17}$ = methyl, R^{14}/R^{16} = -O-, n = 1)

This compound was prepared by epoxidation of Compound **35** (Structure **3** of Scheme I, where $R^9 = R^{13} = R^{15} = R^{18} = R^{19} = R^{20} = R^{21} = H$, $R^8 = R^{10}$ = fluorine, $R^6 = R^{17}$ = methyl, R^{14}/R^{16} = a bond, n = 1) according to a standard procedure as yellow solids: Compound **97**, ^{1}H NMR (500 MHz, acetone-d_6) 7.57 (d, J = 8.5, 1H), 7.35 (ddd, J = 9.2,1.8, 1.8, 1H), 6.88 (ddd, J = 9.5, 2.8, 2.8, 1H), 6.80 (d, J = 8.5, 1H), 5.94 (d, J = 10.4, 1H), 5.77 (s, 1H), 5.61 (s, 1H), 2.65 (s, 1H), 2.27 (d, J = 0.9, 3H), 2.12-2.06 (m,

1H), 1.86-1.80 (m, 1H), 1.76-1.68 (m, 1H), 1.66-1.58 (m, 1H), 1.46-1.40 (m, 1H), 1.37 (s, 3H), 1.36-1.26 (m, 2H), 1.21 (s, 3H), 1.11 (s, 3H).

EXAMPLE 31

Preparation of (±)-*(5l,1'l)*- 5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro-2,2-dimethyl-5*H*-chromeno[3,4-f]quinolin-4-one (Compound 98, Structure 4 of Scheme I, where R^4 = H, R^{17} = methyl, X = O)

These compounds were prepared in a similar fashion as that described in Example 1 general procedure from 3-(dimethylphenylsilyl)-3-methyl-1-cyclohexene (Structure 6 of Scheme I, where R^{17} = methyl, $R^{15} = R^{18} = R^{19} = R^{20} = R^{21}$ = H, n = 1) and 7,9-difluoro-1,2,3,4-tetrahydro-5-methoxy-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinolin-4-one (Compound 99). ^{1}H NMR (500 MHz, $CDCl_3$), 7.55 (d, J = 8.9, 1H), 7.02-6.95 (m, 1H), 6.70-6.64 (m, 1H), 6.66 (d, J = 8.6, 1H), 6.42 (d, J = 5.8, 1H), 5.26 (s, 1H), 4.42 (s, 1H), 2.67 (d, J = 15.2, 1H), 2.56 (d, J = 15.0, 1H), 2.48 (m, 1H), 1.94-1.80 (m, 2H), 1.78-1.66 (m, 2H), 1.44 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.42-1.36 (m, 1H), 1.29-1.25 (m, 1H).

EXAMPLE 32

The in vitro activity of selected hPR modulator compounds of the present invention were evaluated utilizing the cotransfection assay, and in standard receptor competitive binding assays, according to the following illustrative Examples.

Cotransfection assay

The function and detailed preparation procedure of the cotransfection assays have been described previously (Pathirana, C. *et al.*, Nonsteroidal Human Progesterone

Receptor Modulators from the Marine Alga Cymopolia Barbata. *Mol. Pharm.* **1995**, *47*, 630-635). Briefly, the cotransfection assays were carried out in CV-1 cells (African green monkey kidney fibroblasts), which were transiently transfected, by the standard calcium phosphate coprecipitation procedure (Berger, T. S. *et al.*, Interaction of Glucocorticoid Analogues with the Human Glucocorticoid Receptor. *J. Steroid Biochem. Mol. Bio.* **1992**, *41*, 733-738) with the Plasmid containing receptor, MTV-LUC reporter, pRS-β-Gal, and filler DNA (Rous sarcoma virus chloramphenicol acetyltransferase). The agonist activity was determined by examining the LUC expression (normalized response) and the efficacy readout was a relative value to the maximal LUC expression produced by progesterone. All the cotransfection experiments were carried out in 96-well plates by automation (Beckman Biomomek automated workstation).

Receptor Binding Assays

The preparation of receptor binding assays for hPR-A was described in literature (Pathirana, C. *et al.*, Nonsteroidal Human Progesterone Receptor Modulators from the Marine Alga Cymopolia Barbata. *Mol. Pharm.* **1995**, *47*, 630-635.)

The agonist, antagonist and binding activity assay results of selected progesterone receptor modulator compounds of the present invention and the standard reference compounds on PR are shown in Table 1 below. Efficacy is reported as the percent maximal response observed for each compound relative to the reference agonist and antagonist compounds indicated above. Also reported in Table 1 for each compound is its antagonist potency or IC_{50} (which is the concentration (nM), required to reduce the maximal response by 50%), and its agonist potency or EC_{50} (nM), which is the effective concentration that produced 50% of the maximum response.

Table 1: Agonist, antagonist and binding activity of progesterone receptor modulator compounds of present invention and the reference agonist compound, progesterone (Prog), and reference antagonist compound, RU486 and ZK299.

Cmpd	PR Agonist CV-1 Cells		PR Antagonist CV-1 Cells		PR Binding
No.	Efficacy (%)	Potency (nM)	Efficacy (%)	Potency (nM)	K_i (nM)
Prog	100	2.9	na	na	3.5
RU486	na	na	96	0.18	0.58
ZK299	na	na	99	1.6	18
24	168	3.6	na	na	6.4
25	86	9.7	na	na	6.3
27	68	43	na	na	241
28	171	0.9	na	na	2.0
34	164	0.5	na	na	3.7
35	100	5.4	na	na	14
37	na	na	50	113	>1000
38	166	0.6	na	na	1.9
41	122	10	na	na	11
42	27	38	na	na	143
44	123	6.7	na	na	7.7
45	94	9.1	na	na	17
64	na	na	80	1900	485
65	na	na	59	650	329
71	139	3.4	na	na	3.9

na = not active (*i.e.* efficacy of <20 and potency of >10,000)

EXAMPLE 33

The in vivo activity of selected hPR modulator compounds of the present invention were evaluated utilizing the McPhail assay, according to the following illustrative Examples. The Clauberg or McPhail assay is a classic assay utilizing rabbits to measure progestational activity. The reason rabbit is used is because the results observed in rabbit have proved to be a good indicator and predictor of activity in the human. In this assay, immature rabbits are treated initially with estradiol, which induces

growth in the uterus. This is followed by treatment with a progestin, which causes a large change in the glandular content of the uterus. It is this change in the glandular component, which is a measure of the progestational activity of a progestin. The measurement of these glandular changes are carried out histologically using stained sections of the uterus. The assay results of the new 5-cycloalkenyl compounds are tabulated in Table 2. The in vivo potency of the progestins is presented as the minimum active dose (MAD) in mg/kg.

Table 2: The potency (MAD in mg/kg) of selected 5-cycloalkenyl compounds of present invention in the McPhail assay.

Compd #	MAD (mg/kg)	EC_{50} (nM)	K_i (nM)
24	0.25	3.6	6.4
34	0.25	0.5	3.7
38	0.10	0.6	1.9
71	0.25	3.4	3.9

Pharmacological and Other Applications

The following Example provides illustrative pharmaceutical composition formulations:

EXAMPLE 34

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
COMPOUND **24**	10
Starch, dried	100
Magnesium stearate	10
Total	120 mg

The above ingredients are mixed and filled into hard gelatin capsules in 120 mg quantities.

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
COMPOUND 24	10
Cellulose, microcrystalline	200
Silicon dioxide, fumed	10
Stearic acid	10
Total	230 mg

The components are blended and compressed to form tablets each weighing 230 mg.

Tablets, each containing 10 mg of active ingredient, are made as follows:

	Quantity (mg/tablet)
COMPOUND 24	10
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (PVP) (as 10% solution in water)	4
Sodium carboxymethyl starch (SCMS)	4.5
Magnesium stearate	0.5
Talc	1.0
Total	100 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of PVP is mixed with the resultant powders, which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The SCMS, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Suppositories, each containing 225 mg of active ingredient, may be made as follows:

	Quantity (mg/suppository)
COMPOUND **24**	20
Saturated fatty acid glycerides	2,000
Total	2,020 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of normal 2 g capacity and allowed to cool.

An intravenous formulation may be prepared as follows:

	Quantity
COMPOUND **24**	10 mg
isotonic saline	1000 mL
glycerol	100 mL

The compound is dissolved in the glycerol and then the solution is slowly diluted with isotonic saline. The solution of the above ingredients is then administered intravenously at a rate of 1 mL per minute to a patient.

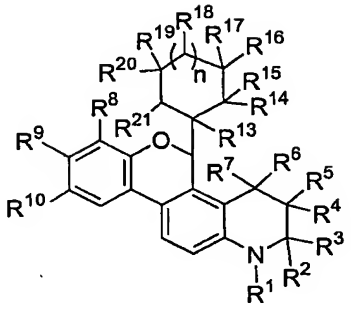
The present invention includes any combination of the various species and subgeneric groupings falling within the generic disclosure. This invention therefore includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

The scope of the invention is not to be limited by the description of the examples. Modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific examples which have been presented by way of example.

What is claimed is:

1. A compound of the formula:



(I)

wherein:

R^1 is selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 haloalkyl, C_1–C_4 heteroalkyl, COR^{11}, CO_2R^{11}, SO_2R^{11}, and $CONR^{11}R^{12}$;

R^2 and R^3 each independently is selected from the group of hydrogen, C_1–C_6 alkyl, and C_1–C_6 haloalkyl; or

R^2 and R^3 taken together form a cycloalkyl ring of from three to twelve carbons;

R^4 through R^7 each independently is selected from the group of hydrogen, F, Cl, Br, CN, OR^{11}, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl; or

R^5 and R^7 taken together form a bond; or

R^6 and R^7 taken together are selected from the group of methylidene, mono-substituted methylidene, di-substituted methylidene and carbonyl;

R^8 through R^{10} each independently is selected from the group of hydrogen, F, Cl, Br, I, NO_2, CN, OR^{11}, $NR^{11}R^{12}$, SR^{11}, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, C_1–C_8 alkyl, C_1–C_8 heteroalkyl, C_1–C_8 haloalkyl, allyl, C_2–C_8 alkenyl and C_2–C_8 alkynyl;

R^{11} and R^{12} each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^{13} is hydrogen; or

R^{13} and R^{14} taken together form a bond;

R^{14} through R^{20} each independently is selected from the group of hydrogen, F, Cl, Br, OR^{11}, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl; or

R^{14} and R^{15} taken together are selected from the group of methylidene, carbonyl and thiocarbonyl; or

R^{16} and R^{17} taken together are selected from the group of methylidene, mono-substituted methylidene, di-substituted methylidene, carbonyl and thiocarbonyl; or

R^{14} and R^{16} taken together form a bond or "–O–" bridge; or

R^{16} and R^{18} taken together form a bond when n is 1; or

R^{16} and R^{19} taken together form a bond when n is 0;

R^{21} is hydrogen; or

R^{21} and R^{20} taken together form a bond;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt or prodrug thereof.

2. A compound according to claim 1, wherein R^1 is selected from the group of hydrogen, C_1–C_4 alkyl, COR^{11}, SO_2R^{11}, and $CONR^{11}R^{12}$.

3. A compound according to claim 1, wherein R^2 and R^3 each independently is selected from the group of C_1–C_4 alkyl, and C_1–C_4 haloalkyl.

4. A compound according to claim 1, wherein

R^5 and R^7 taken together form a bond;

R^4 and R^6 each independently is selected from the group of hydrogen, F, Cl, Br, CN, OR^{11}, C_1–C_4 alkyl, and C_1–C_4 haloalkyl.

5. A compound according to claim 1, wherein

R^6 and R^7 taken together are selected from the group of methylidene, and carbonyl;

R^4 and R^5 each independently is selected from the group of hydrogen, F, and C_1–C_4 alkyl.

6. A compound according to claim 1, wherein R^8 through R^{10} each independently is selected from the group of hydrogen, F, Cl, Br, NO_2, CN, OR^{11}, SR^{11}, C_1–C_6 alkyl, C_1–C_6 heteroalkyl, and C_1–C_6 haloalkyl.

7. A compound according to claim 6, wherein R^8 through R^{10} each independently is selected from the group of hydrogen, F, and OR^{11}.

8. A compound according to claim 1, wherein R^{11} through R^{12} each independently is selected from the group of hydrogen, and C_1–C_4 alkyl.

9. A compound according to claim 1, wherein

R^{14} and R^{16} taken together form a bond or "–O–" bridge;

R^{15}, R^{17}, R^{18}, R^{19}, R^{20} each independently is selected from the group of hydrogen, F, Cl, C_1–C_4 alkyl, and C_1–C_4 haloalkyl.

10. A compound according to claim 1, wherein

R^{16} and R^{17} taken together are selected from the group of methylidene, mono-substituted methylidene, and di-substituted methylidene;

R^{14}, R^{15}, R^{18}, R^{19}, R^{20} each independently is selected from the group of hydrogen, F, Cl, C_1–C_4 alkyl, and C_1–C_4 haloalkyl.

11. A compound according to claim 1, wherein

R^{16} and R^{18} taken together form a bond when n is 1; or

R^{16} and R^{19} taken together form a bond when n is 0;

R^{14}, R^{15}, R^{17}, R^{20} each independently is selected from the group of hydrogen, F, Cl, C_1–C_4 alkyl, and C_1–C_4 haloalkyl.

12. A compound according to claim 1, wherein said compound is selected from the group of:

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **24**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **25**);

(+)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **27**);

(-)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **28**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **29**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **30**);

(+)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **32**);

(-)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **33**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **34**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **35**);

(+)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **37**);

(-)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **38**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-methoxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **39**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **41**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **42**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclopentenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **44**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclopentenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **45**);

(±)-(*5l,1'l*)-5-(3,5,5-trimethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **47**);

(±)-(*5l,1'u*)-5-(3,5,5-trimethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **48**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **50**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **51**);

(±)-5-(3-methyl-3-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **52**);

(±)-5-(2-cyclopenta-1,3-dienyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **53**);

(±)-(*5l,1'l*)-5-(3-ethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **55**);

(±)-(*5l,1'u*)-5-(3-ethyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **56**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-7-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **58**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclohexenyl)-7-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **59**);

(±)-(*5l,1'l*)-5-(3-ethyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **61**);

(±)-(*5l,1'l*)-5-(3-ethylidenecyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **62**);

(±)-(*5l,1'l*)-5-(3-methyl-3-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **63**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-8-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **64**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-8-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **65**);

(±)-(*5l,1'l*)-5-(2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **67**);

(±)-(*5l,1'u*)-5-(2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **68**);

(±)-5-(1-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **69**);

(±)-(*5l,1'l*)-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **71**);

(+)-(*5l,1'l*)-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **73**);

(-)-(*5l,1'l*)-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **74**);

(±)-(*5l,1'l*)-5-(2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **75**);

(±)-(*5l,1'u*)-5-(2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **76**);

(±)-(*5l,1'l*)-5-(2-cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-5*H*-chromeno[3,4-*f*]quinoline (compound **77**);

(±)-(*5l,1'l*)-5-(2-methylidenecyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **79**);

(±)-(*5l,1'u*)-5-(2-methylidenecyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **80**);

(±)-(*5l,1'l*)-5-(2-oxocyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **81**);

(±)-(*5l,1'u*)-5-(2-oxocyclohexyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **82**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-methoxy-1,2-dihydro-1,2,2,4-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **83**);

(±)-5-(2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **84**);

(±)-(*5l,1'l*)-5-(2,3-dimethyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **85**);

(±)-5-(3-methylidene-cyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **87**);

(±)-(*5l,1'u*)-5-(3-ethylidenecyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **88**);

(±)-*(5l,1'l)*- 5-(2-cycloheptenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound 89);

(±)-*(5l,1'l)*- 5-(2-cyclooctenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound **91**);

(±)-*(5l,1'u)*- 5-(2-cyclooctenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound **92**);

(±)-*(5l,1'l)*- 5-(2,3-epoxy-3-methylcyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound **94**);

(±)-*(5l,1'l)*- 5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylene-5*H*-chromeno[3,4-f]quinolin-3-ol (Compound **95**);

(±)-*(5l,1'l)*- 5-(2,3-epoxy-2,3-dimethylcyclopentyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound **96**);

(±)-*(5l,1'u)*- 5-(2,3-epoxy-3-methylcyclohexyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-f]quinoline (Compound **97**); and

(±)-*(5l,1'l)*- 5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro-2,2-dimethyl-5*H*-chromeno[3,4-f]quinolin-4-one (Compound **98**).

13. A compound according to claim 1, wherein said compound is selected from the group of:

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **24**);

(-)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **28**);

(-)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-9-hydroxy-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **33**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **34**);

(±)-(*5l,1'u*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **35**);

(-)-(*5l,1'l*)-5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **38**);

(±)-(*5l,1'l*)-5-(3-methyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **50**);

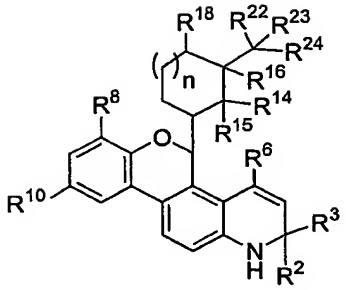
(±)-(*5l,1'u*)-5-(3-methyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **51**);

(±)-(*5l,1'l*)-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **71**);

(-)-(*5l,1'l*)-5-(2,3-dimethyl-2-cyclopentenyl)-7,9-difluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (compound **74**); and

(±)-*(5l,1'l)*- 5-(3-methyl-2-cyclohexenyl)-7,9-difluoro-1,2,3,4-tetrahydro-2,2-dimethyl-5*H*-chromeno[3,4-f]quinolin-4-one (Compound **98**).

14. A compound of the formula:



(II)

wherein:

R^2 and R^3 each independently is selected from the group of hydrogen, C_1–C_4 alkyl, and C_1–C_4 haloalkyl;

R^6 is selected from the group of hydrogen, F, Cl, Br, CN, OR^{11}, C_1–C_4 alkyl, and C_1–C_4 haloalkyl;

R^8 and R^{10} each independently is selected from the group consisting of hydrogen, F, Cl, Br, CN, OR^{11}, $NR^{11}R^{12}$, SR^{11}, COR^{11}, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, C_1–C_4 haloalkyl, allyl, and C_2–C_4 alkenyl;

R^{11} and R^{12} each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^{14}, R^{15}, R^{18}, R^{22}, R^{23}, R^{24} each independently is selected from the group of hydrogen, F, Cl, OR^{11}, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl;

R^{22}, R^{23}, R^{24} together consists of not more than 3 carbon atoms;

R^{16} taken together with one of R^{14}, R^{18}, and R^{22} form a bond or "–O–" bridge;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt or prodrug thereof.

15. A compound according to claim 14, wherein

R^2 and R^3 each independently is selected from the group of C_1–C_4 alkyl;

R^6 is selected from the group of F, Cl, Br, C_1–C_4 alkyl, and C_1–C_4 haloalkyl;

R^8 and R^{10} each independently is selected from the group of hydrogen, F, Cl, Br, CN, OR^{11}, C_1–C_4 alkyl, and C_1–C_4 haloalkyl;

R^{11} and R^{12} each is independently selected from the group of hydrogen, C_1–C_4 alkyl;

R^{14}, R^{15}, R^{18}, R^{22}, R^{23}, R^{24} each independently is selected from the group of hydrogen, F, C_1–C_4 alkyl;

R^{16} taken together with one of R^{14}, R^{18}, and R^{22} form a bond or "–O–" bridge;

n is 0, 1, or 2.

16. A compound according to claim 15, wherein

R^2 and R^3 each independently is CH_3;

R^6 is selected from the group of F, Cl, Br, CH_3, CH_2CH_3, and CF_3;

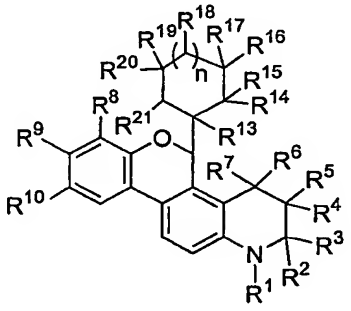
R^8 is hydrogen or F;

R^{10} is selected from the group of hydrogen, F, Cl, Br, CN, OH, OCH_3, CH_3, CH_2CH_3, and CF_3;

R^{14} and R^{16} taken together form a bond or "–O–" bridge;

R^{15}, R^{18}, R^{22}, R^{23}, and R^{24} each independently is hydrogen or CH_3.

17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula:



(I)

wherein:

R^1 is selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 haloalkyl, C_1–C_4 heteroalkyl, COR^{11}, CO_2R^{11}, SO_2R^{11}, and $CONR^{11}R^{12}$;

R^2 and R^3 each independently is selected from the group of hydrogen, C_1–C_6 alkyl, and C_1–C_6 haloalkyl; or

R^2 and R^3 taken together form a cycloalkyl ring of from three to twelve carbons;

R^4 through R^7 each independently is selected from the group of hydrogen, F, Cl, Br, CN, OR^{11}, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl; or

R^5 and R^7 taken together form a bond; or

R^6 and R^7 taken together are selected from the group of methylidene, mono-substituted methylidene, di-substituted methylidene and carbonyl;

R^8 through R^{10} each independently is selected from the group of hydrogen, F, Cl, Br, I, NO_2, CN, OR^{11}, $NR^{11}R^{12}$, SR^{11}, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, C_1–C_8 alkyl, C_1–C_8 heteroalkyl, C_1–C_8 haloalkyl, allyl, C_2–C_8 alkenyl and C_2–C_8 alkynyl;

R^{11} and R^{12} each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^{13} is hydrogen; or

R^{13} and R^{14} taken together form a bond;

R^{14} through R^{20} each independently is selected from the group of hydrogen, F, Cl, Br, OR^{11}, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl; or

R^{14} and R^{15} taken together are selected from the group of methylidene, carbonyl and thiocarbonyl; or

R^{16} and R^{17} taken together are selected from the group of methylidene, mono-substituted methylidene, di-substituted methylidene, carbonyl and thiocarbonyl; or

R^{14} and R^{16} taken together form a bond or "–O–" bridge; or

R^{16} and R^{18} taken together form a bond when n is 1; or

R^{16} and R^{19} taken together form a bond when n is 0;

R^{21} is hydrogen; or

R^{21} and R^{20} taken together form a bond;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt or prodrug thereof.

18. A pharmaceutical composition according to claim 17, wherein R^1 is selected from the group of hydrogen, C_1–C_4 alkyl, COR^{11}, SO_2R^{11}, and $CONR^{11}R^{12}$.

19. A pharmaceutical composition according to claim 17, wherein R^2 and R^3 each independently is selected from the group of C_1–C_4 alkyl, and C_1–C_4 haloalkyl.

20. A pharmaceutical composition according to claim 17, wherein

R^5 and R^7 taken together form a bond;

R^4 and R^6 each independently is selected from the group of hydrogen, F, Cl, Br, CN, OR^{11}, C_1–C_4 alkyl, and C_1–C_4 haloalkyl.

21. A pharmaceutical composition according to claim 17, wherein

R^6 and R^7 taken together are selected from the group of methylidene, and carbonyl;

R^4 and R^5 each independently is selected from the group of hydrogen, F, and C_1–C_4 alkyl.

22. A pharmaceutical composition according to claim 17, wherein R^8 through R^{10} each independently is selected from the group of hydrogen, F, Cl, Br, NO_2, CN, OR^{11}, SR^{11}, C_1–C_6 alkyl, C_1–C_6 heteroalkyl, and C_1–C_6 haloalkyl.

23. A pharmaceutical composition according to claim 22, wherein R^8 through R^{10} each independently is selected from the group of hydrogen, F, and OR^{11}.

24. A pharmaceutical composition according to claim 17, wherein R^{11} through R^{12} each independently is selected from the group of hydrogen, and C_1–C_4 alkyl.

25. A pharmaceutical composition according to claim 17, wherein

R^{14} and R^{16} taken together form a bond or "–O–" bridge;

R^{15}, R^{17}, R^{18}, R^{19}, R^{20} each independently is selected from the group of hydrogen, F, Cl, C_1–C_4 alkyl, and C_1–C_4 haloalkyl.

26. A pharmaceutical composition according to claim 17, wherein

R^{16} and R^{17} taken together are selected from the group of methylidene, mono-substituted methylidene, and di-substituted methylidene;

R^{14}, R^{15}, R^{18}, R^{19}, R^{20} each independently is selected from the group of hydrogen, F, Cl, C_1–C_4 alkyl, and C_1–C_4 haloalkyl.

27. A pharmaceutical composition according to claim 17, wherein

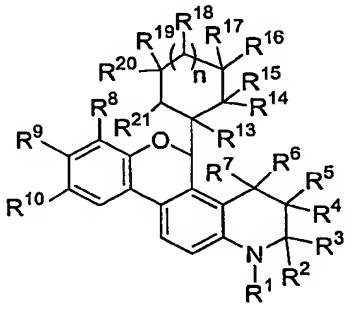
R^{16} and R^{18} taken together form a bond when n is 1; or

R^{16} and R^{19} taken together form a bond when n is 0;

R^{14}, R^{15}, R^{17}, R^{20} each independently is selected from the group of hydrogen, F, Cl, C_1–C_4 alkyl, and C_1–C_4 haloalkyl.

28. A method of treating an individual having a condition mediated by a progesterone receptor comprising administering to said individual a pharmaceutically effective amount of a compound according to any one of claims 1, 12 or 14.

29. A method of treating an individual having a condition mediated by a progesterone receptor comprising administering to said individual a pharmaceutically effective amount of a compound represented by formula (I):



(I)

wherein:

R^1 is selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 haloalkyl, C_1–C_4 heteroalkyl, COR^{11}, CO_2R^{11}, SO_2R^{11}, and $CONR^{11}R^{12}$;

R^2 and R^3 each independently is selected from the group of hydrogen, C_1–C_6 alkyl, and C_1–C_6 haloalkyl; or

R^2 and R^3 taken together form a cycloalkyl ring of from three to twelve carbons;

R^4 through R^7 each independently is selected from the group of hydrogen, F, Cl, Br, CN, OR^{11}, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl; or

R^5 and R^7 taken together form a bond; or

R^6 and R^7 taken together are selected from the group of methylidene, mono-substituted methylidene, di-substituted methylidene and carbonyl;

R^8 through R^{10} each independently is selected from the group of hydrogen, F, Cl, Br, I, NO_2, CN, OR^{11}, $NR^{11}R^{12}$, SR^{11}, COR^{11}, CO_2R^{11}, $CONR^{11}R^{12}$, C_1–C_8 alkyl, C_1–C_8 heteroalkyl, C_1–C_8 haloalkyl, allyl, C_2–C_8 alkenyl and C_2–C_8 alkynyl;

R^{11} and R^{12} each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^{13} is hydrogen; or

R^{13} and R^{14} taken together form a bond;

R^{14} through R^{20} each independently is selected from the group of hydrogen, F, Cl, Br, OR^{11}, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl; or

R^{14} and R^{15} taken together are selected from the group of methylidene, carbonyl and thiocarbonyl; or

R^{16} and R^{17} taken together are selected from the group of methylidene, mono-substituted methylidene, di-substituted methylidene, carbonyl and thiocarbonyl; or

R^{14} and R^{16} taken together form a bond or "–O–" bridge; or

R^{16} and R^{18} taken together form a bond when n is 1; or

R^{16} and R^{19} taken together form a bond when n is 0;

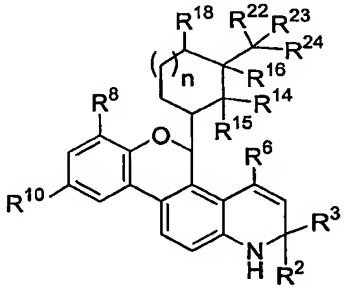
R^{21} is hydrogen; or

R^{21} and R^{20} taken together form a bond;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt or prodrug thereof.

30. A method of treating an individual having a condition mediated by a progesterone receptor comprising administering to said individual a pharmaceutically effective amount of a compound represented by formula (II):



(II)

wherein:

R^2 and R^3 each independently is selected from the group of hydrogen, C_1–C_4 alkyl, and C_1–C_4 haloalkyl;

R^6 is selected from the group of hydrogen, F, Cl, Br, CN, OR^{11}, C_1–C_4 alkyl, and C_1–C_4 haloalkyl;

R^8 and R^{10} each independently is selected from the group of hydrogen, F, Cl, Br, CN, OR^{11}, $NR^{11}R^{12}$, SR^{11}, COR^{11}, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, C_1–C_4 haloalkyl, allyl, and C_2–C_4 alkenyl;

R^{11} and R^{12} each is independently selected from the group of hydrogen, C_1–C_4 alkyl, C_1–C_4 heteroalkyl, and C_1–C_4 haloalkyl;

R^{14}, R^{15}, R^{18}, R^{22}, R^{23}, R^{24} each independently is selected from the group of hydrogen, F, Cl, OR^{11}, C_1–C_4 alkyl, C_1–C_4 haloalkyl, and C_1–C_4 heteroalkyl;

R^{22}, R^{23}, R^{24} together consists of not more than 3 carbon atoms;

R^{16} taken together with one of R^{14}, R^{18}, and R^{22} form a bond or "–O–" bridge;

n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt or prodrug thereof.

31. A method according to claim 28, wherein said condition is selected from the group of dysfunctional uterine bleeding, dysmenorrhea, endometriosis, leiomyomas (uterine fibroids), hot flushes, mood disorders, meningiomas, hormone-dependent cancers and female osteoporosis.

32. A method according to claim 28, wherein said condition is alleviated with female hormone replacement therapy.

33. A method of modulating fertility in an individual comprising administering to said individual a pharmaceutically effective amount of a compound according to any one of claims 1, 12 or 14.

34. A method of providing contraception to an individual comprising administering to said individual a pharmaceutically effective amount of a compound according to any one of claims 1, 12 or 14.

35. A method of modulating a progesterone receptor in an individual comprising administering to said individual a compound according to any one of claims 1, 12, or 14 in an amount effective to modulate a progesterone receptor.

36. A method according to claim 35, wherein said modulation is activation.

37. A method according to claim 36, wherein said compound provides at least 50% maximal activation of the progesterone receptor at a concentration of less than 100 nM.

38. A method according to claim 36, wherein said compound provides at least 50% maximal activation of the progesterone receptor at a concentration of less than 50 nM.

39. A method according to claim 36, wherein said compound provides at least 50% maximal activation of the progesterone receptor at a concentration of less than 20 nM.

40. A method according to claim 36, wherein said compound provides at least 50% maximal activation of the progesterone receptor at a concentration of less than 10 nM.

41. A method of treating cancer, comprising administering to a patient in need thereof an effective amount of a compound according to any one of claims 1, 12 or 14.

42. A method according to claim 41, wherein said cancer is selected from the group of ovarian cancer, breast cancer, endometrium cancer and prostate cancer.

43. A method of determining the presence of a progesterone receptor (PR) in a cell or cell extract comprising (a) labeling a compound according to any one of claims 1, 12 or 14; (b) contacting the cell or cell extract with said labeled compound; and (c) testing the contracted cell or cell extract to determine the presence of progesterone receptor.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/24419

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D491/04 A61K31/47 //(C07D491/04,307:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 02565 A (ABBOTT LAB ;LIGAND PHARM INC (US)) 10 January 2002 (2002-01-10) examples 131,133,136,137,140-143,144,146,148-150,152-170,209,212,220-222,224,225,236-243,246,247,252,253,263-265,270-273... ---	1-11, 17-27
X	WO 99 41256 A (ABBOTT LAB ;LIGAND PHARM INC (US)) 19 August 1999 (1999-08-19) cited in the application examples ...277,284,288,291,297,299,302,303,319,325,340,341,375,390-393,414,415,417-420,422,441 --- -/--	1-11, 17-27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 January 2004	29/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Frelon, D

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 41257 A (ABBOTT LAB ;LIGAND PHARM INC (US)) 19 August 1999 (1999-08-19) cited in the application overlapping	1-11, 17-27
Y	LIN ZHI ET AL: "5-ARYL-1,2-DIHYDROCHROMENOÄ3,4-FÜQUINOLINES: A NOVEL CLASS OF NONSTEROIDAL HUMAN PROGESTERONE RECEPTOR AGONISTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 41, no. 3, 1998, pages 291-302, XP002161933 ISSN: 0022-2623 chart 2	1-43
Y	TEGLEY C M ET AL: "5-BENZYLIDENE 1,2-DIHYDROCHROMENOÄ3,4-FÜQUINOLINES, A NOVEL CLASS OF NONSTEROIDAL HUMAN PROGESTERONE RECEPTOR AGONISTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 41, no. 22, 1998, pages 4354-4359, XP002161937 ISSN: 0022-2623 table 1	1-43
Y	ZHI L ET AL: "5-alkyl 1,2-dihydrochromeno'3,4-f!quinolines: a novel class of nonsteroidal progesterone receptor modulators" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3365-3370, XP004143759 ISSN: 0960-894X table 1	1-43
A	ZHI L ET AL: "NOVEL CLASS OF NON-STEROIDAL PROGESTERONE RECEPTOR ANTAGONISTS" EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 9, no. 6, 1999, pages 695-700, XP001094162 ISSN: 1354-3776 page 697	1-43

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/24419

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 28-43 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/24419

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